VOLUME 60 NUMBER 1

THE JOHN CRERAR LIBRARY
AUG -5 1949

ARCHIVES
OF
DERMATOLOGY AND SYPHILOLOGY

EDITORIAL BOARD

PAUL A. O'LEARY, Chief Editor
102 Second Avenue S. W., Rochester, Minn.

HERBERT RATTNER, Associate Editor, Chicago

HAROLD N. COLE, Cleveland
H. E. MICHELSON, Minneapolis
FRED D. WEIDMAN, Philadelphia
GEORGE M. MacKEE, New York

J. LAMAR CALLAWAY, Durham, N. C.

JULY 1949

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $10.00

Entered as Second Class Matter Oct. 30, 1917, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

COPYRIGHT, 1949, BY THE AMERICAN MEDICAL ASSOCIATION

CONTENTS OF PREVIOUS NUMBER

JUNE 1949. NUMBER 6

Treatment of Early Syphilis with Penicillin Injection in Oil and Wax U. S. P.: Report of One Hundred and Fifty-Three Cases. Louis Chargin, M.D.; Nathan Sobel, M.D.; Charles Rein, M.D., and Theodore Rosenthal, M.D., New York.

Scleroma: Review of Literature and First Report of Multiple Familial Occurrence in the United States. Paul R. Kline, M.D., New York, and Edwin R. Brody, M.D., Youngstown, Ohio.

Mammalian Tyrosinase: Melanin Formation by Ultraviolet Irradiation. Thomas B. Fitzpatrick, M.D., Rochester, Minn.; A. Bunsen Lerner, M.D., Ph.D., Cleveland; Evan Calkins, M.D., Baltimore, and William H. Summerson, Ph.D., Army Chemical Center, Md.

Massive Metastasizing Meningioma Involving the Scalp. Carl W. Laymon, M.D., Minneapolis, and Frederic T. Becker, M.D., Duluth, Minn.

Balanitis Xerotica Obliterans: Report of a Case. David G. Welton, M.D., and Preston Nowlin, M.D., Charlotte, N. C.

Roentgen Therapy for Hyperhidrosis: Observation of One Hundred and Twenty-Two Patients. J. Borak, M.D.; J. J. Eller, M.D., and W. D. Eller, M.D., New York.

Persistent Multiple Herpes-Like Eruption: Response to Repeated Intradermal Injections of Smallpox Vaccine. Leonard E. Savitt, M.D., and Samuel Ayres Jr., M.D., Los Angeles.

Clinical Notes:

A Bullous Eruption Associated with Carcinoma of the Penis. John M. Siegel, M.D., Allentown, Pa.

Ringworm of the Scalp Due to Microsporum Audouini During Pregnancy. Fritz B. Reif, M.D., Niagara Falls, N. Y.

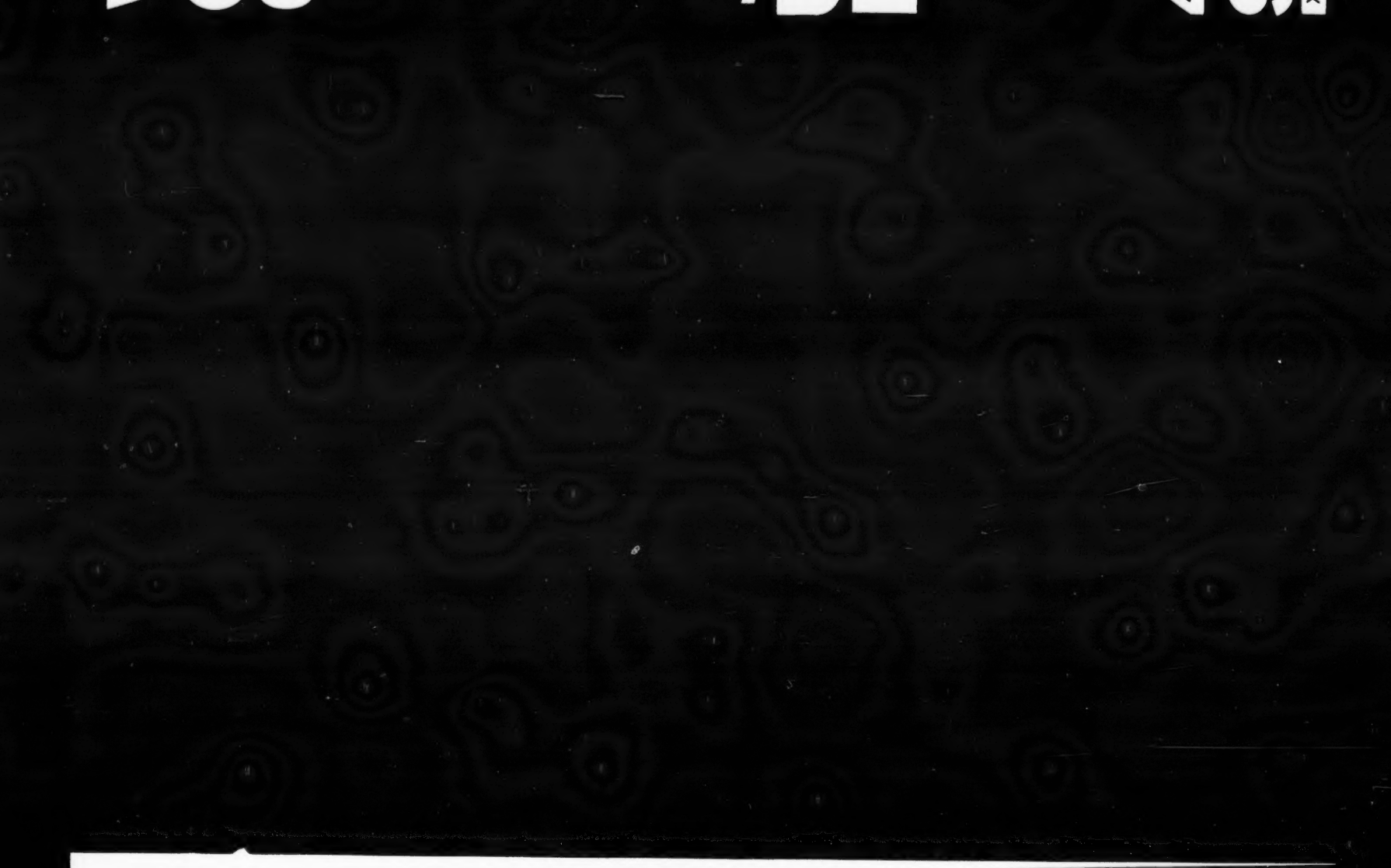
Contact Dermatitis from Streptomycin. Samuel J. Levin, M.D., and Selma S. Moss, M.D., Detroit.

Solid Carbon Dioxide Therapy for Cystic Acne. Carroll S. Wright, M.D., and E. R. Gross, M.D., Philadelphia.

Lead-Containing Clay for Shielding in Roentgen Ray Treatment of the Skin. Robert Kaldeck, M.D., Lowell, Mass.

Concurrent Fungous Infection of the Skin: Report of a Case. Edward P. Cawley, M.D., and S. F. Horne, M.D., Ann Arbor, Mich.

General Index.



Archives of Dermatology and Syphilology

VOLUME 60 JULY 1949 NUMBER 1

COPYRIGHT, 1949, BY THE AMERICAN MEDICAL ASSOCIATION

PODOPHYLLOTOXIN

MAURICE SULLIVAN, M.D.
BALTIMORE

CONDYLOMATA acuminata undergo rapid involution after the topical application of resin of podophyllum.[1] During involution there are profound morphologic changes in the epithelial cells, the most characteristic of which changes is manifested in the enlarged, swollen cell containing finely reticulated, palely basophilic cytoplasm and dispersed chromatin material showing some type of chromosomal arrangement; other changes are seen in various degenerative forms ranging from slight cytoplasmic vacuolation and nuclear alterations to severe degenerative forms manifested by intensely eosinophilic homogeneous cytoplasm and pyknotic nuclei, as well as severely vacuolated cells with absent nuclei.[2] These changes are also noted in the normal skins and mucous membranes of men, rabbits and mice after the application of the drug.

Soon after it was shown[3] that the cytologic effects of resin of podophyllum on epithelial cells are similar to those produced by colchicine, several investigators reported arrest of mitosis in cells of plants, starfish eggs, experimental mouse tumors and tissue cultures. Sullivan

---

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif. April 26, 1948.

Work done in part under a grant-in-aid from the American Cancer Society on recommendation of the Committee on Growth of the National Research Council.

From the Division of Dermatology of the Department of Medicine and the Department of Pharmacology of the Johns Hopkins University School of Medicine and the United States Marine Hospital.

1. (*a*) Kaplan, I. W.: Condylomata Acuminata, New Orleans M. & S. J. **94**:338, 1942. (*b*) Culp, O. S., and Kaplan, I. W.: Condylomata Acuminata: Two Hundred Cases Treated with Podophyllin, Am. J. Surg. **120**:251, 1944.

2. (*a*) King, L. S., and Sullivan, M.: Effects of Podophyllin and of Colchicine on Normal Skin, on Condyloma Acuminatum and on Verruca Vulgaris: Pathologic Observations, Arch. Path. **43**:374 (April) 1947. (*b*) Sullivan, M., and King, L. S.: Effects of Resin of Podophyllum on Normal Skin, Condylomata Acuminata and Verrucae Vulgares, Arch. Dermat. & Syph. **56**:30 (July) 1947.

3. King, L. S., and Sullivan, M.: The Similarity of Podophyllin and Colchicine Effects and the Use of These Drugs in the Treatment of Condylomata Acuminata, Science **104**:244, 1946.

and Wechsler [4] investigated the meristematic tissue of the root tips of Allium cepa immersed in a solution of resin of podophyllum. Pronounced cytologic effects were produced in late prophase, and the spindle mechanism was impaired, as no orientation of the chromosomes on the metaphase plate was observed. Chromosomes were dispersed in the cell. Metaphase chromosomes were in the form of typical chromosomes, sister chromatids held together at the spindle attachment region with slightly contracted arms which had become disengaged from the relational coil. There was an increase in the number of mitotic figures up to metaphase and then a decrease and later complete absence of anaphase and telephase figures. The effects of resin of podophyllum on the maturation and cleavage of the starfish egg were studied by Cornman,[5] who found that the meiotic and mitotic spindles were quickly inactivated by podophyllin. Belkin [6] and Hartwell and Shear [7] produced severe damage of mouse tumor cells in vivo. Ormsbee, Cornman and Berger [8] found that the effect of podophyllin in tissue cultures was to damage selectively and prevent the growth of mouse tumors L946 and MA387; in vivo studies in tumor-bearing mice by these authors [8] confirmed the presence of selective tumor damaging effects which they had first noted in tissue culture preparations of the same tumors.

The ability of resin of podophyllum to cure condylomata acuminata, its cancerocidal potentialities and its usefulness as a tool for cytologic research make it a drug of considerable interest. Inasmuch as resin of podophyllum is a complex resinous mixture containing many ingredients, it is important to determine the substance or substances in it which are responsible for its biologic activity. The purpose of this paper is to present data showing that of the ingredients of resin of podophyllum now available to me for testing, podophyllotoxin is the only one capable of curing condyloma acuminatum and is the component principally responsible for producing the nuclear alterations and other cytologic changes similar to those produced by podophyllin.

---

4. Sullivan, B. J., and Wechsler, H. I.: The Cytological Effects of Podophyllin, Science **105**:433, 1947.

5. Cornman, I.: The Effects of Podophyllin on the Maturation and Cleavage of the Starfish Egg, Biol. Bull. **93**:214, 1947.

6. Belkin, M.: Effect of Podophyllin on Transplanted Mouse Tumors, Federation Proc. **6** (pt. 2):308, 1947.

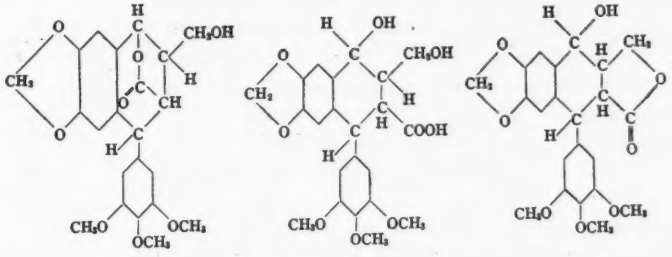
7. Hartwell, J. L., and Shear, M. J.: Cancer Research, to be published.

8. Ormsbee, R. A.; Cornman, I., and Berger, R.: Effects of Podophyllin on Tumor Cells in Tissue Culture, Proc. Soc. Exper. Biol. Med. **66**:586, 1947.

Resin of podophyllum N. F. is the resin or extract of the plant Podophyllum peltatum.[9] The method of its preparation stated in the United States Pharmacopoeia is as follows:

Exhaust with alcohol by slow percolation 100 Gm. of powdered podophyllum; evaporate the percolate to a thin syrup; pour the syrup into 1,000 cc. of water containing 10 cc. of hydrochloric acid, cooled below 10 C.; decant the clear liquid from the settled precipitate; wash the preparation twice with two portions (each of 1,000 cc.) of cold distilled water; dry the resin and powder it.

The resulting product, is an amorphous powder, light brown to greenish, turning dark on exposure to light or when heated above 25 C. It forms a slightly opalescent, faintly acid solution with alcohol, is partially soluble in chloroform and ether and practically insoluble in cold water. It is soluble in normal solutions of potassium hydroxide and of sodium hydroxide. Resin of podophyllum contains podophyllotoxin, podophylloresin, quercetin, α-peltatum and probably other as



Structural formulas of podophyllotoxin (*1*) and its two products of alkaline hydrolysis, podophyllic acid (*2*) and picropodophyllin (*3*).

yet unidentified components. Table 1 illustrates the method employed for the isolation of all the known components of resin of podophyllum except α-peltatum, a crystalline substance which was isolated recently by chromatography.

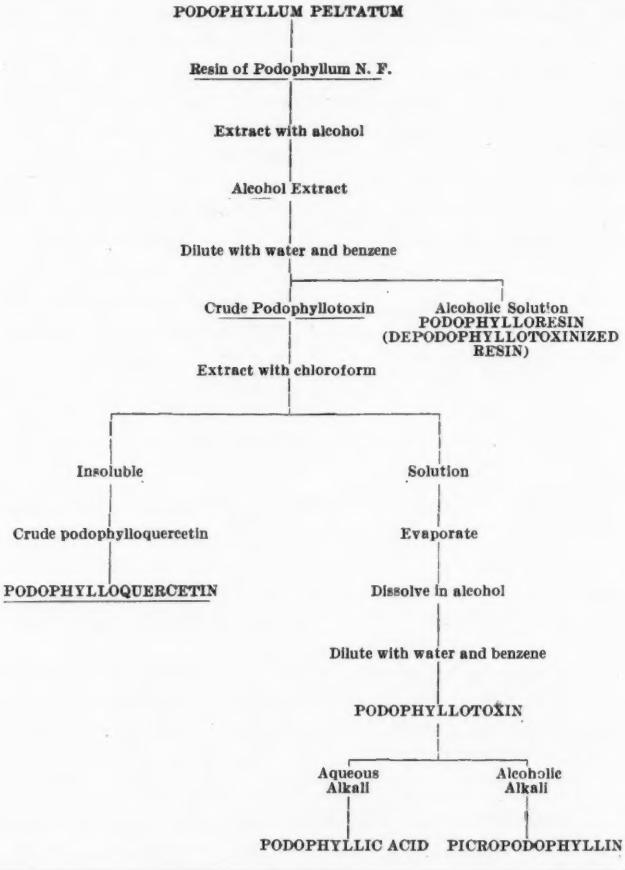
PODOPHYLLOTOXIN

In 1880 Podwyssotzki isolated podophyllotoxin in noncrystalline form from Podophyllum peltatum and Podophyllum emodi, and in

9. (*a*) Pharmacopœia of the United States of America, ed. 11, Easton, Pa., Mack Printing Company, 1936, pp. 294 and 319. (*b*) Wood, G. B., and Bache, F.: The Dispensatory of the United States of America, ed. 21, Philadelphia, J. B. Lippincott Company, 1926, vol. 20, p. 879. (*c*) Blumgarten, A. S.: Textbook of Materia Medica, Pharmacology and Therapeutics, ed. 7, New York, The Macmillan Company, 1937, pp. 220 and 223. (*d*) Viehover, A., and Mack, H.: Biochemistry of the May Apple Root (Podophyllum Peltatum), J. Am. Pharm. A. **27**:632, 1938.

1891 Kuersten succeeded in crystallizing it.[10] As noted in table 1, crude or amorphous podophyllotoxin is obtained by treatment of the alcoholic extract with water and benzene. Crystalline podophyllotoxin

TABLE 1.—*The Method Employed for the Isolation of Podophyllotoxin*



is obtained by extracting crude podophyllotoxin with chloroform, evaporating the solution, dissolving the remaining compound in alcohol

10. (*a*) Podwyssotzki, V.: Pharmakologische Studien über Podophyllum Peltatum, Arch. f. exper. Path. u. Pharmakol. **13**:29, 1880-1881; (*b*) Ueber die wirksamen Bestandtheile des Podophyllin's, Ber. d. deutsch. chem. Gesellsch. **15**:377, 1882. (*c*) Kewisten: Arch. d. Pharm. **229**:220, 1891, cited by Viehover and Mack.[9d]

and diluting it with water and benzene. The podophyllotoxin content of commercial resin of podophyllum varies from 28.2 to 52.6 per cent.[11] The structure of podophyllotoxin, $C_{22}H_{22}O_8$, was established by the investigations of Spath and associates and Borsche and Nieman.[12] Until recently it was the only crystallizable substance occurring as such in the resin. It is characterized physically by a melting point of 114 to 117 C. and decided polymorphism, and chemically by two crystalline products of alkaline hydrolysis (see table 1 and figure). When podophyllotoxin (figure, *1*) is treated with dilute aqueous alkali the lactone ring within the molecule is opened and the alkaline salt of podophyllic acid is secured. Podophyllic acid (figure, *2*) is characterized by thick, colorless prismatic needles, a melting point of 147 C. and solubility in cold absolute and 95 per cent alcohol, acetone, slight solubility in ether and insolubility in petroleum benzine and water. Careful acidification of the solution causes podophyllic acid to precipitate. If it is precipitated in the presence of chloroform, an optically active product is secured. If an alkaline alcohol solution of podophyllotoxin is heated, rearrangement occurs within the podophyllotoxin molecule (figure, *1*) and picropodophyllin (figure, *3*) is obtained. Physically picropodophyllin is characterized by long, fine, colorless, silky needles, a melting point of 228 C. and insolubility in cold alcohol and water. This compound is optically inactive.

PODOPHYLLORESIN (DEPODOPHYLLOTOXINIZED RESIN)

Podophylloresin is obtained (table 1) from the alcoholic solution remaining after the precipitation of crude podophyllotoxin when the resin is again precipitated in the alcoholic solution by means of diluted mineral acids. Podophylloresin is a dark brown, amorphous mass containing a mixture of resin glycosides, resenes, starches, gums and other unidentified plant materials.

QUERCETIN

When crude podophyllotoxin is extracted with chloroform there is obtained an insoluble fraction (table 1) as well as the soluble fraction from which the podophyllotoxin is crystallized. Quercetin is derived

11. Wood and Bache.[9b] Warren, L. E.: Assay of Resin of Podophyllum, J. A. Off. Agric. Chemists **13**:117, 1930.

12. (*a*) Spath, E.; Wessely, F., and Nadler, E.: Zur Konstitution des Podophyllotoxins und Pikropodophyllins, Ber. d. Deutsch. chem. Gesellsch. **66**:1773, 1932; **65**:125, 1933. (*b*) Spath, E.: Wessely, F., and Kornfeld, L.: Ueber die Konstitution von Podophyllotoxin und Pikropodophyllin, ibid. **65**:1536, 1932. (*c*) Borsche, W., and Nieman, J.: Ueber Podophyllin, ibid. **65**:1633, 1932; (*d*) Zur Konstitution des Podophyllotoxins und Pikropodophyllins, ibid. **65**:1846, 1932; Ueber Podophyllin, Ann. d. Chem. **494**:1245, 1932; **499**:59, 1932; **502**:264, 1933.

from the chloroform-insoluble fraction; it is a yellow crystalline powder, with a melting point of 312 to 314 C. when anhydrous, and is soluble in absolute alcohol and in alkali hydroxides. According to Dunstan and Henry [13] this pigment, which is largely responsible for the color of resin of podophyllum, has physical and chemical properties identical with those of quercetin from oak bark. Whether quercetin occurs in partial combination with other constituents of the drug, in the form of glucosides or otherwise, has not been decided.[9b]

ALPHA-PELTATUM (N.C.I. 1074)

Recently Hartwell [14] isolated a new compound, α-peltatum (N.C.I. 1074 [14a]) in pure form from resin of podophyllum by chemical fractionation involving solvent extraction and chromatographic absorption on alumina (aluminum oxide) in a yield of about 9 per cent. A-peltatum crystallizes from alcohol in colorless, transparent prisms and has a melting point of 230.5 to 232.5 C. (corrected). Solutions of the pure substance in alcohol and benzene exhibit a strong blue fluorescence under ultraviolet light in distinction from solutions of podophyllotoxin, which have only a slight blue fluorescence. The compound has mouse tumor–necrotizing property.

During investigation of the clinical effects of resin of podophyllum, it was found that the drug cured a high percentage of condylomata acuminata when it was applied in powder form, made into a paste with water, incorporated in ointments or suspended in oil.[2b] In one series of patients treated with a 25 per cent concentration of the drug in liquid petrolatum, a few chronic and partially cornified perianal condylomas failed to undergo involution; also verrucae vulgares were resistant to resin of podophyllum in oil in each of 100 cases. It appeared that perhaps the failure of the resin to penetrate the thickly keratinized perianal tumors and verrucae vulgares may have been due to the nonpenetrating quality of the suspending material, oil. Alcoholic solutions of resin of podophyllum were then employed in an attempt to afford better penetration. Results in another series of patients with condylomata acuminata treated with a 20 per cent concentration of resin of podophyllum in 95 per cent alcohol were superior to those obtained with the oil suspension, much of which spread from the surface of the warts to the adjacent normal tissue; the tincture penetrated the

13. Dunstan, W. R., and Henry, T. A.: J. Chem. Soc. London **72**:209-226, 1898, cited by Viehover and Mack.[9d]

14. Hartwell, J. L.: A New Compound Isolated from Podophyllum Peltatum, J. Am. Chem. Soc. **69**:218, 1947.

14a. National Cancer Institute 1074.

crevices of the surfaces of the tumors and confined itself precisely to the tumors, if it was applied accurately in small amounts. Cures resulted in 15 of 100 patients with verrucae vulgares who were treated with the resin in alcohol. These results prompted a trial of other solvents. It seemed likely that a solvent which dissolved keratin would probably enhance the action of the drug and render it effective against the verruca vulgaris as well as against the moist, nonkeratinized or only slightly keratinized genital wart. Consequently various percentages of resin of podophyllum were dissolved in normal solutions of potassium hydroxide and of sodium hydroxide, and these alkaline solutions were found to be inert when applied to condylomata acuminata,

TABLE 2.—*Results of Successful Treatment in 16 Cases of Condyloma Acuminatum With Alcoholic Solutions of Crude Noncrystalline Podophyllotoxin*

Percentage of Podophyllotoxin	Location	Number of Patients Treated	Number of Applications Necessary for Cure
0.5	Penis	3	3,2,1
5	Penis	9	1,1,1,1,1,1,1,1,1
5	Perianal region	1	2
10	Penis	3	3,2,1

TABLE 3.—*Results of Successful Treatment in 41 Cases of Condyloma Acuminatum With Alcoholic Solutions of Crystalline Podophyllotoxin*

Percentage of Podophyllotoxin	Location	Number of Patients Treated	Number of Applications Necessary for Cure
5	Penis	9	4,3,2,1,1,1,1,1,1
5	Perianal region	2	5,2
5	Vulva	1	2
10	Penis	26	5,4,4,3,3,3,3,3,2, 2,2,2,2,2,1,1,1,1, 1,1,1,1,1,1,1,1,1
10	Perianal region	3	7,5,3

verrucae vulgares and normal skin. Thus the substance or substances in the resin responsible for curing condyloma acuminatum could be rendered ineffective by solution in potassium hydroxide and in sodium hydroxide, and it was suspected [15] that the component concerned was podophyllotoxin because, as was previously noted, podophyllotoxin is easily susceptible to alkaline hydrolysis.

To test the supposition that podophyllotoxin is the component responsible for curing condylomata acuminata, patients with the disease were treated with solutions or suspensions of all the presently available components of resin of podophyllum and the products of the alkaline

15. Sullivan and King.[2b] King and Sullivan.[3] Sullivan, M., and Blanchard, K. C.: Podophyllotoxin: Preliminary Note, Bull. Johns Hopkins Hosp. **81**:65, 1947.

hydrolysis of podophyllotoxin, namely, commercial noncrystalline or crude podophyllotoxin, crystalline podophyllotoxin, picropodophyllin, podophyllic acid, podophylloresin and quercetin. Seventy patients were treated with podophyllotoxin. Sixteen, or 80 per cent, of 20 patients treated with noncrystalline commercial podophyllotoxin [16] were cured. Forty-one, or 82 per cent, of 50 patients treated with crystalline podophyllotoxin [17] were cured. Thus, the crude amorphous podophyllotoxin and crystalline podophyllotoxin cured 54, or 81 per cent, of 60 patients with condylomata acuminata. The successful results of treatment with podophyllotoxin are summarized in tables 2 and 3. Picropodophyllin [17] was applied to condylomata acuminata in 15 cases; podophyllic acid,[17] in 6 cases; podophylloresin,[17] in 8 cases, and quercetin,[17] in 23 cases. There was no therapeutic response to the last-mentioned four compounds. These findings prove that of the constituents of resin of podophyllum tested, podophyllotoxin is the only one capable of curing condyloma acuminatum. It should be pointed out, however, that at the time of writing, α-peltatum is not available. When it is released its effect on condylomata acuminata will be evaluated. Unpublished reports from other laboratories have indicated that there may be other mitosis-inhibiting compounds in resin of podophyllum; these will also be tested for their effects on condylomata acuminata and on normal skin, when they become available.

The ability to cure condylomata acuminata is only one phase of the biologic activity of podophyllin. Characteristic erythematous, edematous reactions in normal skin are reproducible and vary in severity with the amount and concentration of the drug, the length of exposure and the location of the application. Thus, in one series of 100 men there were 30 positive reactions to patch tests with 0.2 cc. of a 25 per cent concentration of resin of podophyllum in liquid petrolatum elicited [20] after twenty-four hours of contact; in another group of 100 men 69 positive reactions to patch tests with 0.2 cc. of the same suspension were elicited. It is likely that a higher percentage of positive reactions would occur on more prolonged contact. To determine the percentage of positive reactions to smaller amounts of podophyllin in weaker concentration, patch tests with 0.001 cc. of 1 and of 10 per cent solutions of resin of podophyllum in alcohol were applied to the forearms or arms of 60 men. Positive reactions were elicited for only 8 per cent. The site of the application, as well as the amount and concentration, is of importance. On glabrous skin, or in areas where there is no pressure or apposition of a flexural or overlying skin surface, the reaction is always less intense than that which occurs in a location

16. Supplied by Dr. Milton Bush and Dr. Kenneth Blanchard.

17. Supplied by Dr. W. G. Bywater of the S. B. Penick Company.

such as the coronal sulcus of an uncircumcised man or in the groin or the perianal region. The reaction of the skin varies from the mildest manifestation of punctate erythema to intense erythema, edema and superficial ulceration. Cutaneous reactions produced with relatively large (0.2 cc.) or with small amounts (0.001 cc.) are identical in appearance, varying in size and intensity only. The histologic reaction described elsewhere in detail [2a] may be summarized briefly as follows: The cells of the upper prickle cell layer of the epidermis are swollen; the intercellular bridges frequently are absent, and the cell membranes are accentuated and heavily stained. Keratohyalin granules from the stratum granulosum are often dispersed within these enlarged cells. The cytoplasm stains palely, and a delicate linear reticulum is seen. Some of the prickle cells are vacuolated, the nuclei being pyknotic and surrounded by large, clear halos. In the deeper prickle cell layers and in or just above the basal cell layer are found numerous cells with distorted or aborted mitotic figures. Many of these cells are larger than adjacent normal cells. Cytoplasm is often pale and faintly basophilic and composed of prominent though faintly staining reticulum. The nuclei are absent, and nuclear material is either dispersed as blue-staining dots or rods or clumped together in bizarre patterns. In addition to the cells with disturbed mitotic phases there are cells with bright eosinophilic cytoplasm and pyknotic or karyorrhectic nuclei. In the cutis there is edema of variable amount, its extent depending on the severity of the reaction and the site of the application; there is variable round cell infiltration which is principally perivascular but which may also be diffuse.

Skin tests with 0.001 cc. of 1 and of 10 per cent concentrations of resin of podophyllum, podophyllotoxin, picropodophyllin, podophylloresin and quercetin were applied to the normal skin of the arms or forearms of 60 patients. No reactions were produced by picropodophyllin, podophylloresin or quercetin. Positive reactions for 8 per cent of the patients were produced by resin of podophyllum, and for 8 per cent by podophyllotoxin, there thus being established a parallelism of resin of podophyllum and of podophyllotoxin reactions on normal skin. Alcoholic solutions of podophyllotoxin were then applied to the prepuces of 7 men twenty-four, forty-eight and seventy-two hours before circumcision. Also biopsy specimens were taken from the sites of positive reactions to skin tests with podophyllotoxin after twenty-four, forty-eight and seventy-two hours in 3 rabbits and from the site of a forty-eight hour positive reaction to tests with podophyllotoxin in normal human skin; from penile warts in 2 patients and from molluscum contagiosum lesions in 2 patients, these 4 persons having been treated forty-eight hours previously with podophyllotoxin. Micro-

scopic examination of the human and rabbit specimens disclosed epidermal changes identical to those produced by resin of podophyllum. Solutions and suspensions of picropodophyllin, podophyllic acid, quercetin and podophylloresin were applied to the foreskins of 4 patients forty-eight hours before circumcision and to rabbits' backs twenty-four and forty-eight hours before the sites of application were excised for microscopic examination. There were either slight or no epidermal changes in the areas treated with podophyllic acid, podophylloresin and quercetin. In the skins treated with picropodophyllin there were occasional epidermal cells exhibiting abnormal mitotic figures.

COMMENT

Although the data here presented prove that podophyllotoxin is the component in resin of podophyllum responsible for curing condylomata acuminata and for arresting mitosis of epidermal cells, it is possible that in the resin there are substances other than podophyllotoxin which possess biologic activity of a similar or of a different type. It is unsettled whether the same mechanism operates in the cure of condylomata acuminata and in the arrest of experimental tumors of the mouse, but probably it does, because the microscopic changes of involuting experimental tumors are similar to those noted in involuting condylomata acuminata.

Podophyllotoxin is only very slightly soluble in water.[9b] Ormsbee and Cornman [17a] described an experiment by Rhoads in which 1 cc. of a water extract of resin of podophyllum was administered to a mouse, bearing sarcoma 180; generalized pyknosis of the tumor quickly followed. It may possibly be adduced from this observation that there is a water-soluble, tumor-necrotizing substance in resin of podophyllum which is not podophyllotoxin. Also it was demonstrated by Sullivan and Wechsler [4] that resin of podophyllum, in saturated aqueous solution and in filtrates of such solutions, caused mitotic poisoning of the root tips of Allium cepa, this occurrence indicating the existence of a water-soluble substance capable of inhibiting mitosis. The possibility that traces of podophyllotoxin may have been present in the preparations of Rhoads [8] and of Sullivan and Wechsler [4] must not be overlooked in evaluating their findings.

After investigating the effects of the components of resin of podophyllum on the inhibition of arbacia egg cleavage Cornman [18] concluded that the combined effects of podophyllotoxin and of quercetin were responsible for the powerful inhibition of cleavage which can be produced

17a. Ormsbee, R. A., and Cornman, I.: Personal communication to the author.

18. Cornman, I.: Inhibition of Arbacia Egg Cleavage by Podophyllotoxin and Related Substances, Biol. Bull. **93**:192, 1947.

by resin of podophyllum. The findings of Rhoads,[8] Sullivan and Wechsler [4] and Cornman [18] introduce the impression that in resin of podophyllum there are substances other than podophyllotoxin which possess biologic activity of a type similar to that of podophyllotoxin. Quercetin is now being investigated in several other laboratories, and unpublished reports have indicated that this component may have some extremely promising biologic properties of another type. There is also unpublished evidence from other laboratories that quercetin obtained from resin of podophyllum may not be identical with the quercetin obtained from oak bark. Preliminary toxicity studies in our laboratory indicate that quercetin from oak bark may be the same compound as podophylloquercetin. The biologic activity of α-peltatum is being investigated by Hartwell [14] and his collaborators, and a future report from this group may supply proof of biologic activity similar to or different from that of podophyllotoxin. A-peltatum has tumor-necrotizing properties.[14] When it becomes available in sufficient quantity for investigation this compound should be tested for its effect on condylomata acuminata and on normal skin, as it is of interest to determine whether components of resin of podophyllum with tumor-necrotizing properties possess selective tumor cell–damaging properties or whether they affect normal epidermal cells and the epithelial cells of other tumors.

The possibility that resin of podophyllum and podophyllotoxin exert an influence directly on the virus responsible for the growth of condylomas has been considered and is now being investigated. Our preliminary observations indicate that this approach will probably be unsuccessful because of unsurmountable technical difficulties. Aside from its significance in the evaluation of resin of podophyllum it would be desirable to learn whether the drug has a viricidal action, as clinicians constantly question whether or not cornified warts and moist genital warts have a common origin. The fact that resin of podophyllum and podophyllotoxin cure condylomata acuminata and are ineffective on verrucae vulgares has been advanced as proof that the two types of warts are due to different viruses.[19] It is likely that they are not, as there is evidence [20] proving the common etiology of the dry cornified wart and the moist genital wart.

Resin of podophyllum and podophyllotoxin are less toxic than is colchicine and are of interest in the field of cancer research. A promising approach to the chemotherapy of cancer may be in the isolation of other less toxic components of resin of podophyllum or isomers of podophyllotoxin which manifest tumor-necrotizing ability.

---

19. McCarthy, C. L., in discussion on Sullivan and King.[2b]

20. Van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, Oxford University Press, 1940, p. 133.

SUMMARY AND CONCLUSIONS

Resin of podophyllum, the resin of Podophyllum peltatum, is a complex resinous mixture of known and unknown substances. The identified components are as follows: podophyllotoxin (with its two products of alkaline hydrolysis, podophyllic acid and picropodophyllin), podophylloresin, quercetin and α-peltatum (N. C. I. 1074).

Resin of podophyllum topically applied to condylomata acuminata cures them. Condylomata acuminata were treated with all the presently available components of the resin. Podophyllotoxin was the only component capable of curing the genital warts.

Resin of podophyllum topically applied to skin and benign epithelial tumors produces severe cytotoxic effects and interference with mitosis, resulting in distorted mitotic patterns. Of the presently available components of the resin, podophyllotoxin is apparently the one principally responsible for the production of the abnormal cellular alterations.

11 East Chase Street.

ABSTRACT OF DISCUSSION

Dr. H. L. Keim, Detroit: It is gratifying, I am sure, to all of us to find that Dr. Sullivan is continuing his studies with this interesting drug. In a previous communication, read before this group two years ago, he offered us an improved clinical procedure by suggesting 95 per cent alcohol as a vehicle for resin of podophyllum.

He also pointed out at that time that the dramatic response of condyloma acuminatum to resin of podophyllum could not be explained with the simple assumption that the drug produces a spasm of the small vessels, which in turn results in ischemia, necrosis and sloughing. He indicated then, and has since unquestionably demonstrated, that the resin of podophyllum and now podophyllotoxin possess a biologic activity which characteristically exerts a profound effect on the function of the cell by arresting mitosis in the metaphase. The investigation of the possible use of the drug in treatment of cancer naturally followed, to which work with the cells of plants, starfish eggs, experimental mouse tumors and tissue cultures Dr. Sullivan has referred.

It is interesting to note the extent of growth control on neoplastic cells as obtained by Belkin in a series of experiments. He used Swiss mice carrying 15 day old implants of mouse sarcoma (CR 180), which were given subcutaneous injections of resin of podophyllum in sesame oil in doses of "20 m.p.k." every 3.4 days for two weeks. At this time the tumor size in mice treated with resin of podophyllum, as expressed by the terminal volumes, was about one-seventh that of the controls. In a similar experiment, with the use of a transplantable mammary adenocarcinoma, in the C_3H strain, the terminal values of the treated tumors were two-thirds those of the controls. The microscopic changes were similar to those encountered in epithelial cells treated with resin of podophyllum, the characterstic nuclear changes being a diminution of the number of mitotic figures.

As Dr. Sullivan has said, the ability of resin of podophyllum to cure condylomas, its cancerocidal potentialities and its usefulness as a tool for cytologic research make it a drug of considerable interest. Now that podophyllotoxin has been

shown to be the active fraction, it is to be hoped that Dr. Sullivan and others will continue to investigate this new dermatologic tool in both benign and malignant new growths.

DR. FRED WEIDMAN, Philadelphia: The similarity in the histology of verruca vulgaris and condyloma acuminatum naturally raises the question as to whether podophyllotoxin would be effective in verruca vulgaris also. I have heard that it has been uniformly unsuccessful. The histology of condyloma acuminatum in the regressive stages is particularly similar to that of verruca vulgaris. However, in the acute, lush stage there is the addition of edematous, inflammatory features, and the biology of the epithelial cells may be different then from that in the late stage. If one could get the cells of verruca vulgaris into a comparable proliferative state, by means such as applying croton oil, treatment with resin of podophyllum might be effective.

DR. MARION SULZBERGER, New York: This is a most interesting and fundamental paper, and all the studies that have been carried out by Dr. Sullivan and his co-workers are of the greatest interest, not only to dermatologists, but to those working in many other branches of medicine. It appears to me that the arrest of the mitotic figures in a certain phase might provide a method for treating not only warts, as Dr. Weidman said, but also epitheliomas. Is it not true that the phase of mitotic division seen here as a result of treatment with resin of podophyllum is one which is particularly sensitive to radiation? If this is true, it is conceivable that, with doses of podophyllotoxin which are insufficient in themselves to cure, one may render the dividing cells of epitheliomas and other tumors much more radiosensitive than they were before. My associates and I are now engaged in a series of experiments at the New York Skin and Cancer Unit to see whether or not resin of podophyllum and other substances actually render the normal skin, as well as tumors, more sensitive than before the effects of roentgen rays and other radiation; and, if so, in just what way this sensitivity is shown and may be used. We believe that our results may be of significance and perhaps some day of value in the combined treatment of cancer.

DR. SAMUEL AYRES JR., Los Angeles: With reference to Dr. Weidman's remarks, I have been interested in trying to convert certain verrucae vulgares into lesions comparable to condylomas. I have been doing it by applying monochloroacetic acid. After the dead skin has been trimmed away, a succulent lesion remains and resin of podophyllum, 25 per cent, dissolved in acetone, may be applied. I have had some degree of success, but the lesions do not respond as well as condylomas do. Sometimes one can accomplish more with both applications than with either alone.

A CLINICAL APPRAISAL OF THE COLD WAVE PROCESS

MILTON H. COHEN, M.D.
YORK, PA.

IN 1938 Goodman [1] reported damage to hair by a "home permanent wave." Areas of complete baldness developed in his patient, and he stated that there was no warning on the package of the possibility of any bad result. In 1941, Bunce, Parker and Lewis [2] reported a death following administration of a heatless permanent wave at a beauty shop. They concluded that the clinical course shown by the patient and the pathologic changes seen at autopsy were identical with those occurring in reported cases of acute poisoning with hydrogen sulfide. They showed that the material present in the curling solution was also present in the patient's blood at the time of death. Examination of the curling solution revealed the presence of ammonium sulfide. After this report the Food and Drug Administration took immediate action, and ammonium sulfide was outlawed for use in "cold wave" solutions.

The cold wave process had such an appeal to women who desire a wave in the hair when nature does not supply it that soon various substitute chemicals were employed. At the present time, the active ingredient of the majority of the cold wave solutions is thioglycolic acid, ($HS.CH_2$-$COOH$). Ammonia, perfume and coloring matter are also present. Solutions for home use have the same ingredients in smaller proportions. Ideally, the acid content should be from 4 to 7 per cent, and the p_H, between 9.0 and 9.5.[3] However, reports soon began to appear of damage to the hair and scalp accompanying the use of thioglycolic acid solutions. Howell [4] described a case of dermatitis venenata of the face, neck and ears following cold permanent waving. In 1946,

1. Goodman, H.: Damage to Hair by a Home "Permanent," Urol. & Cutan. Rev. **42**:124 (Feb.) 1938.

2. Bunce, A. H.; Parker, F. P., and Lewis, G. T.: Accidental Death from Absorption of Heatless Permanent Wave Solution, J. A. M. A. **116**:1515 (April 5) 1941.

3. Council on Pharmacy and Chemistry, American Medical Association: Personal communication to the author, March 2, 1948.

4. Howell, J. B.: Contact Dermatitis from Cold Permanent Waving, Arch. Dermat. & Syph. **49**:432 (June) 1944.

Cotter [5] described 5 cases, "from a large group," with the production of various degrees of dermatitis, hepatic damage and toxic reactions following the application of the cold wave process. He stated that thioglycolic acid can cause severe allergic reactions in sensitive persons, and that, as is true with other allergens, the main impact is on the skin and mucous membranes. The effect is cumulative, and sufferers have remissions after contact with the acid has ceased. The process has been applied to many thousands without ill effects, but it is possible that repeated exposures may eventually prove disastrous to those who have been previously immune. In general, persons with anemia and allergic disturbances have been the most vulnerable. Cotter expressed the conclusion that, now that the product is being sold in chain stores, its indiscriminate use will result in an increased incidence of poisonings. Adequate labeling and understanding of the dangers involved are imperative. An editorial in *The Journal of the American Medical Association* [6] commented on Cotter's article by emphasizing the fact that fifty different commercial agencies are engaged in the manufacture of materials used in the cold wave process, with no definite standards as to what is safe or harmful; and that it is time for public recognition of the fact that as much careful evidence needs to be accumulated regarding the safety of substances placed on the surface of the body as concerning those taken into its interior. Unquestionably, if not thioglycolic acid, at least the hydrogen sulfide, or some of the other chemicals associated with this process, can produce severe allergic reactions in sensitive persons. McGill and Rag [7] reported 2 cases of dermatitis, and Goodman [8] in 1945 added other examples to those cited in his previous article.

It would thus seem that the cold wave process has dangerous potentialities and, with its increasing widespread use fostered by extensive advertising, should arouse the concern of dermatologists and other physicians. The general public has some realization of the possible harm of these products, and often a patient asks the question, "Will a cold wave harm me?" What should the dermatologist or general practitioner answer?

---

5. Cotter, L. H.: Thioglycolic Acid Poisoning in Connection with the "Cold Wave" Process, J. A. M. A. **131**:592 (June 15) 1946.

6. Effects of the Cold Wave Process, editorial, J. A. M. A. **131**:746 (June 29) 1946.

7. McGill, C. M., and Rag, L.: Cold Wave Dermatitis: Report of Two Cases, Indust. Med. **16**:238 (May) 1947.

8. Goodman, H.: Dermatitis from Cold Wave Permanent Chemicals. Urol. & Cutan. Rev. **49**:117 (Feb.) 1945.

A group of investigators have expressed the belief that the cold wave process is innocuous. McCord [9] stated that no primary irritation of the skin occurs as a result of contact with thioglycolic acid or its alkaline derivatives in a concentration below 8 per cent by volume; and he [10] found no evidence of sensitivity, or allergic responses of the skin to carefully prepared ammonium thioglycolate. Cappel and Cappel [11] reported the incidence of injurious effects observed from 30,000,000 or more applications of the cold wave process to be under 0.1 per cent. Goldman, Mason and McDaniel [12] stated that, in a personal communication, H. Rattner had indicated that there had been only about 22 complaints among 50,000 treatments. McNally and Scull [13] stated the conclusion, after dermatologic studies on 154 human subjects and toxicologic studies on rats and guinea pigs, that the cold wave solution containing 6.5 per cent ammonium thioglycolate is nontoxic when applied in a prescribed manner. Goldman and associates [12] found that the frequency of reactions was reported to be less than 0.1 per cent.

Because of the complicated nature of the cold wave process, in which various chemicals are applied in succession, it is difficult to determine which particular ingredient was the probable factor in producing irritation of the skin. Goldman and associates [12] suggested that for correct analysis multiple skin testing should be performed with the preliminary shampoo material, the preliminary cleansing lotion, the cold wave solution, the oxidizing agent, the post-treatment shampoo material, the wave-setting material and perfumes, among other items employed in the process. Making the problem more difficult, Goodman [8] expressed the belief that the patch test is not reliable with cold wave preparations, since the dermatitis is usually due to a combination of thioglycolic acid with the softener, the fixative or the keratin, rather than the thioglycolic acid itself. The type of investigation required to fix responsibility is rather formidable for the average dermatologist or general practitioner, and I am convinced that many cases of cold wave dermatitis are unrecognized. Since the advent of

9. McCord, C. P.: Toxicity of Thioglycolic Acid Used in Cold Wave Permanent Process, J. A. M. A. **131**:776 (June 29) 1946.

10. McCord, C. P.: The Physiologic Properties of Thioglycolic Acid and Thioglycolates, Indust. Med. **15**:669 (Dec.) 1946.

11. Cappel, N. A., and Cappel, L. R.: Cold Permanent Wave Solutions as an Irritant, Am. Perfumer & Essential Oil Rev. **48**:43 (Aug.) 1946.

12. Goldman, L.; Mason, L., and McDaniel, W.: Permanent Wave Process, J. A. M. A. **137**:354 (May 22) 1948.

13. McNally, W. D., and Scull, R. H.: Thioglycollate Cold Wave Process, Arch. Dermat. & Syph. **57**:275 (Feb.) 1948.

the cold wave process that can be self applied and the application of strong sensitizing agents to many types of skin by the general public, many more injuries than the estimated 0.1 per cent must be produced. Quite often the first application will produce no damage, and a false sense of security is initiated; and, when a rash appears after the second, or third, or an even later, application, the damage is not attributed to any ingredient used in the cold wave process. Three case histories will illustrate this point.

REPORT OF CASES

CASE 1.—Mrs. G. R., aged 34, applied a home permanent wave in June 1947. She noted some burning and tingling of her scalp and fingers; however, this reaction subsided in a few days, and she did not consult a physician. In January 1948 she sought relief for a painful erythematous, vesicular eruption, with cracking of the skin on the fingers of both hands. She worked as a proofreader, and it was assumed that she had an occupational dermatitis. However, patch tests with the various inks and other contactants had negative results. She had also used two common household cleansers, but reactions to patch tests with these materials in 1:10 dilution were also negative. Her rash improved under treatment with simple compresses. In March 1948 a severe exacerbation, which was extremely painful and responded poorly to any therapy, occurred. After a few weeks of unsuccessful treatment the patient volunteered the information that she had applied a second home permanent wave two days before the eruption appeared in January and had applied a similar permanent wave to a friend one day before the exacerbation in March. A patch test with the suspected wave solution gave a 3 plus reaction.

CASE 2.—Mrs. C. T., aged 39, consulted me in April 1948 for an exudative, eczematoid eruption, which had been present since January 1948, on both ears. She was treated, with good results, with soothing compresses, but in two weeks an acute exacerbation, which caused her to be hospitalized, occurred on her ears, arms, back and legs. The rash consisted of vesicles and papules arranged in groups, with erythema. Biopsy, reported by Dr. Fred Weidman, of the University of Pennsylvania, showed the epidermis to be acanthotic, with obliteration of the papillae of the interpapillary pegs and thickening of the hair follicles. In the corium a minor inflammatory reaction appeared in the form of a mantle of edema around congested blood vessels. Eosinophils were scattered. Dr. Weidman stated that the specimen was inadequate to supply a definitive diagnosis of any specific dermatologic entity, unless it were lichenification. The patient then stated that three days prior to the appearance of the rash on her ears she had given a home permanent wave but that she had not volunteered this information because she had used a similar solution twice before with no ill effects. The day before she had suffered the acute exacerbation, she had applied a "rinse," which she had also used previously, to her hair. Patch tests with the cold wave solution and with the rinse were negative, but testing with a combination of the two materials gave a 3 plus reaction.

CASE 3.—Mrs. R. B., aged 25, consulted me in May 1948 for an acute erythematovesicular eruption on her face and hands. After the 2 previous cases, I had become "cold wave conscious," and I did not wait until she volunteered information. In answer to my question concerning the use of a cold wave process,

she stated that she had given a friend a home permanent wave in January 1948 and in March 1948, with no ill effects. The day after she had administered one to herself the acute eruption had appeared. Patch tests with the cold wave solution gave a 2 plus reaction in forty-eight hours.

Another type of injury is obvious to the operator, the patient and the physician—the direct contact dermatitis. Beauty parlor operators are particularly susceptible, and in the past two years I have treated 10 patients whose cases follow the general pattern outlined in the following report:

CASE 4.—C. C., aged 20, consulted me in April 1947 for a discrete, pruritic, vesicular eruption of the fingers and dorsum of both hands, which condition had been present for two weeks. She had been a beauty operator for three years but had changed her position one week before the onset of the rash. In her new place of employment she had been applying cold permanent waves constantly, whereas in her former position she had applied only machine permanent waves. She remained away from work for two weeks, and with the use of soothing compresses the rash healed fairly well. Within twenty-four hours of the patient's return to work, at which time she again applied cold wave solutions, the eruption reappeared in an intensified form. Patch test of the cold wave solution she had been applying gave a 3 plus reaction. It required considerably more time to heal this second reaction. In June 1947 the patient again attempted to work with the cold wave solution, using protective creams, but a severe reaction again occurred. She finally decided to seek another form of employment, and in September 1947 the rash was completely healed.

This form of occupational eczema is now well recognized. Schwartz, Tulipan and Peck,[14] in their second edition of "Occupational Diseases of the Skin," stated that dermatitis in hairdressers may result from the primary irritant effects of the alkaline substances, or an allergic contact dermatitis may be produced by the resins, or both developments may take place. Goldman and associates [12] and Cotter [5] described the manifestations completely, and Beek [15] noted the same type of cold wave dermatitis in the Netherlands. He performed patch tests with thioglycolic acid on 100 women and 20 men and found "considerable irritation" in 3 per cent of the women and 1 per cent of the men.

The solitary deep burn type of lesion, usually on the hair line of the posterior portion of the neck, was occasionally seen with the machine permanent wave process, but with the recent widespread use of the home permanent cold wave process this reaction has been seen with increasing frequency. In the following case report this lesion is described:

14. Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, Philadelphia, Lea & Febiger, 1947, p. 330.

15. Beek, C. H.: Eczema Caused by Thioglycolic Acid Used in "Cold Wave" Process, Nederl. tijdschr. v. geneesk. **91**:2500, 1947.

CASE 5.—Mrs. E. S., aged 27, was given her third home cold wave on April 1, 1948, yearly intervals having come between the administrations. She noted considerable tingling and burning of her scalp. The next day she consulted me for an erythematous, crusted eruption on the hair line of her forehead and neck. Under soothing wet dressings, the rash quickly cleared and subsided, with no scarring. This reaction could be explained either by faulty technic or by increased sensitivity of her skin due to previous applications of cold wave processes at yearly intervals.

In the beauty shop, when the client complains of burning and tingling, the operator is prone to apply the neutralizing solution as soon as possible, but with the home permanent waves this solution is often considered an essential part of the curling process, and its application is delayed. Many of these reactions are trivial and heal quickly, so that the woman does not see a physician, and it is possible that the next application will produce a pronounced irritant effect.

I hesitate to describe the following group of cases because I am unable scientifically to prove the connection of the cold wave process with various types of eruptions, but I do have the clinical impression that thioglycolic acid solution can have a sensitizing effect in initiating or aggravating various dermatoses. The following cases are examples:

CASE 6.—Mrs. F. E., aged 37, gave a home permanent wave in July 1947. The next day, she suffered severe headaches, and evanescent wheal-like lesions appeared on her forehead, cheeks, breasts and abdomen. She consulted me in August 1947 and presented the picture of chronic urticaria. She had been taking no drugs and had no history of any food sensitivity in the past. Under treatment with antihistaminic drugs and calamine lotion, the lesions slowly resolved, and the patient was free from any urticarial manifestation in one month. In January 1948, she gave another home permanent wave and within six hours again suffered a severe headache, with recurrence of the urticarial lesions. A patch test with the cold wave solution gave a negative reaction. The blood count was normal; there was no eosinophilia, but the cephalin flocculation reaction was 3 plus. The hives persisted for two months and slowly cleared. In March 1948 the patient was completely relieved and the cephalin flocculation reaction was negative.

CASE 7.—Mrs. A. B., aged 30, gave a home permanent wave in December 1947. Within forty-eight hours she noted a brown patch of pigmentation, which persisted, on her forehead. She consulted me in May 1948, and the lesion impressed me as a berlock dermatitis. She gave no history of the use of toilet water, cologne or perfume. Patch test with a cold wave solution gave a 1 plus reaction in forty-eight hours. She had been taking no drugs, laxatives or other possible agents that would produce a fixed eruption. The appearance of this pigmentation after the use of the cold wave process, of course, could be purely coincidental; but some possibility of cause and effect cannot be completely ignored.

CASE 8.—Mrs. R. K., aged 27, consulted me in January 1948 for an eruption, consisting of scaly, dry, yellowish patches, on her scalp, ears, forehead and eyebrows. Serous exudation was present in the postauricular area. The scalp

showed many denuded, crusted lesions, with pronounced seborrhea. The obvious diagnosis of seborrheic eczema was made. The patient stated that she had noted "dry dandruff" for several years but never had experienced this acute eruption until October 1947, when she had had a home permanent wave for the first time. Three days later she had noted itching of her scalp; "pimples" had appeared on her forehead and ears, and gradually scales and crusted lesions had formed. A patch test with the permanent wave solution gave a 2 plus reaction after forty-eight hours.

To ascribe the production of seborrheic eczema to thioglycolic acid on the basis of 1 case would indeed be stretching a theory far; however, I have seen 3 similar cases in which the occurrence of seborrheic eczema shortly followed the application of a home cold wave process. The factor of coincidence cannot be eliminated, but I am advising any patient of mine with seborrhea not to apply a chemical solution if she desires a wave in her hair. The seborrheic soil is there, and it is conceivable that thioglycolic acid may be one of many elusive factors that can produce the seborrheic eczema complex.

I have also recently observed 2 cases of psoriasis that showed an appreciable exacerbation after use of the home permanent wave process, and 1 case of alopecia areata which developed shortly after the giving of a home permanent wave and was similar to the case reported by Goodman.[1] When it is realized that over 30,000,000 home permanent wave kits are sold every year, and when the large number of cases of seborrheic eczema, psoriasis and alopecia areata that are observed is borne in mind, it certainly seems proper to assume that the use of the cold wave process shortly before the appearance of such a rash could be purely coincidental. Any form of *post hoc, ergo propter hoc* reasoning must be eliminated before a correct evaluation can be made, and it will require much more investigation before the exact degree of damage to the skin by thioglycolic acid can be accurately determined. However, I do feel that when one takes a history of a patient affected with dermatitis venenata, eczematoid dermatitis, seborrheic eczema, psoriasis or alopecia areata, for example, the question of a cold wave should receive more than casual consideration.

COMMENT

At the present time considerable confusion exists in the minds of physicians concerning the public health hazard of the thioglycolic acid type of permanent waving. At the meeting of the American Academy of Dermatology and Syphilology in Chicago in December 1947, this problem was brought before a discussion group, headed by Dr. M. B. Sulzberger, and the comments ranged from "completely harmless"

to "a grave danger." I communicated with the committee on cosmetics of the Council on Pharmacy and Chemistry of the American Medical Association [8] and received the following information:

The majority of complaints of both patrons and operators are probably due to misuse of the product or a failure to heed proper directions and precautions. Except in the case of sensitive persons, the judicious use of these solutions should prove a relatively innocuous procedure. However, the fact still remains that unfavorable and sometimes serious reactions do apparently occur. Unfortunately, reports of these cases are not published in scientific and medical literature. We hear about these informally and indirectly. This committee is continuing its accumulation of information which will further enable us to arrive at a fair estimate of the status of these cold wave solutions. It is apparent that "sensitive" persons do suffer unfavorable reactions, although these mishaps are few when one considers the millions of "cold waves" given each year.

Goldman and associates [12] concluded their informative article by stating that the reported frequency of reactions is less than 0.1 per cent, but that the reactions on the hands of the beauty parlor operators are more frequent by far, severer and more extensive than those which occur among the patrons. They offer the beauty operator seven suggestions for prophylaxis—which recommendations seem to substantiate the theory of the harmful tendency of ammonium thioglycolate solution but are utterly impossible for the average woman who gives a home permanent wave to follow.

It seems to me, from a clinical angle, that, in the evaluation of the public health hazard, a distinction should be made between the irritation produced by a permanent wave process given by a competent, well trained beautician and that produced by one given by the average woman at home. I would advise any interested physician to read the list of directions contained in a home permanent wave package. It consists of several sections of instructions in small print which it would require a trained intellect to follow. The list ends with an admonition for the user to read every word of the directions before proceeding, but does not mention any possible cutaneous hazard or give any warning of tingling, burning or other abnormal sensation of the scalp. However, the user is also cautioned somewhat as follows:

Parents! Keep waving lotion and neutralizer where children cannot reach them. Do not let anyone drink the waving lotion or the neutralizing solution.

See that the waving lotion does not come in contact with your eyes, nostrils or mouth.

Avoid spilling the lotion on clothing, furniture, linoleum or the like, as stains may result.

I feel that to introduce into the home such strong chemicals is certainly a potential health hazard. For the average woman to place such chemicals in close contact with the scalp may produce more damage

than a stain on the linoleum. The manufacturers of the home permanent wave process state that the cold wave, when properly given, is a genuine permanent wave and will last until the hair grows out and that the average head of hair is ready for a new wave in three to four months. I feel that it is most difficult to give a home permanent wave properly, and I question the advisability of repeating this process every three months. There is enough reason to believe that repeated application of thioglycolic acid to the scalp will produce sensitization in many cases and direct irritation to the fingers of the applicator in many more. Even the investigators who claim the cold wave process to be harmless [16] emphasize "proper application" and "careful checking for skin irritation." I very much doubt whether the average woman can follow the aforementioned warnings. Furthermore, McNally and Scull [13] concluded their article by remarking that only licensed and experienced operators should handle these solutions; and Goldman and associates [12] stated that little hope is held for the protection of the hands of the beauty parlor operators unless they will consent to wear some sort of protective gloves. Certainly, this hazard also exists for the home user, applying a home permanent wave process every three months and possibly helping her friends between these applications.

CONCLUSIONS

After reviewing the literature and considering my clinical experience, when a patient asks me the question, "Will a cold wave harm me?" I expect to give the following answers:

The home permanent cold wave process is potentially dangerous and may produce various types of irritation of the skin, such as direct contact damage to the fingers, direct contact damage to the scalp and eczematous sensitization of the skin not directly in contact with the solution. It may also be a questionable factor in irritating or exacerbating other dermatoses.

The danger of the cold wave process is lessened if the wave is given by a licensed, competent beautician. The complicated directions can be more carefully followed; signs of irritation can be better observed and neutralization solutions more quickly applied; the procedure will not be repeated so often, and the operator can better protect her own hands.

The cold wave process should not be given to allergic persons, to those suffering from anemia or hepatic disease or to any woman affected with a chronic dermatosis or preceding irritation of the scalp.

---

16. McCord.[9] McCord.[10] Cappel and Cappel.[11] McNally and Scull.[13]

SUMMARY

A review of the literature concerning the cold wave process is given, and 8 case reports are offered to illustrate various types of cutaneous damage consequent to the administration of the thioglycolic acid type of permanent wave process. It is suggested that the permanent wave process used at home is dangerous and hazardous; but that in the hands of a competent beautician it may cause minimal harm in carefully selected cases. If women feel that curl in their hair adds to their beauty, the safest procedure in acquiring it appears to be the machine permanent wave process, and then the cold wave process administered by a careful operator, with the greatest danger of harming their skin coming from the self administration of the home cold wave process.

206 East Market Street.

FOUNDING AND FIRST MEETING OF THE AMERICAN DERMATOLOGICAL ASSOCIATION

A Milestone in the Progress of American Dermatology

PAUL E. BECHET, M.D.
ELIZABETH, N. J.

MY REASON for presenting this subject is purely altruistic. I realize that the proper milieu for it would be the centennial celebration of the Association in 1976, but by that time I may be attending a meeting of the Intercelestial Dermatological Congress, under the presidency of Ernest Bazin, and listening to a complicated discussion by Unna, Walter Highman and Andrew R. Robinson as to the microscopic observations in a particular section of skin. I have therefore prepared the following data for the benefit of the man who will have the great honor of presenting this subject again twenty-eight years from tonight.

In contemplating the founding of the Association and the achievements of its founders, one is compelled by the very strength of character of the men involved to lay aside the motley and assume the attitude of respect, admiration and love which their superlative work in dermatology compels in the heart and mind of every thoughtful man. They did not like dermatology; they loved it and served it all their lives, always considering the beloved specialty first, and themselves last. Dühring did not have abstracts presented to him once a year in convenient form and carefully indexed, and so he prepared them himself, in longhand, pinning the sheets on old samples of wall paper. His old trunk filled with these abstracts can be found in Dr. Fred Weidman's laboratory at the University of Pennsylvania. George Henry Fox was not content with the grotesque colored plates of his time but at his own expense beautifully photographed forty-eight different diseases of the skin, writing two pages of text for each photograph, and received the promise of E. B. Treat & Co. that after 2,000 copies had been sold he would receive the munificent sum of $225. I have in my collection the original agreement for the publication of Fox's famous "Photographic Illustrations of Skin Diseases," signed by him and E. B. Treat & Co. and kindly given me by his son, Howard Fox. This agreement is dated March 24, 1879, and

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 26, 1948.

reposes in my first edition of the work (1879-1880).[1] The first sentence of the preface is worth repeating. "The study of skin diseases without cases or colored plates is like the study of osteology without bones, or the study of geography without maps."

These two examples are only a small fraction of the amount of work done not only by these two particular men but also by the overwhelming majority of the founders. They lived in the Golden Age of clinical dermatology, when expertness in diagnosis was based on the careful observation of thousands of patients exhibiting the many-faceted variations of both the ordinary and the rare dermatoses. All patients were stripped and thoroughly inspected, voluminous notes were taken, the senses of sight and touch became extremely acute, and the coordination of those parts of the mind covering memory, analysis and differentiation so developed that this happy combination brought about a clinical acumen unusual in the present day of coldness, indifference and lack of appreciation of the tremendous achievements of clinical dermatology alone.

FOUNDING OF THE AMERICAN DERMATOLOGICAL ASSOCIATION

Philadelphia was a busy city in 1876. The centennial celebration of the United States in that year and the International Exposition in Fairmont Park were marked by tremendous activity. The American Medical Association and the International Medical Congress met in Philadelphia in the same year, and the intense interest manifested in the future meeting of the section of dermatology and syphilology of the International Medical Congress aroused the enthusiasm of George Henry Fox of New York, Louis A. Dühring of Philadelphia, Lunsford P. Yandell Jr. of Louisville, Ky., L. D. Bulkley of New York, Edward Wigglesworth of Boston and I. E. Atkinson of Baltimore sufficiently to cause them to meet informally on June 7, 1876, in the rooms of the Section on Practical Medicine of the American Medical Association and discuss the feasibility of establishing a national dermatologic society. It was decided that a meeting for organization be held at the University of Pennsylvania, Philadelphia, on Wednesday, Sept. 6, 1876, at 6 p. m. A letter to that effect was mailed to about fifty physicians, in various parts of the United States who were interested in dermatology and was signed by the six aforementioned men. Twenty-three of the physicians invited responded to the call, but only fourteen were present at the organization meeting. They were I. E. Atkinson, Baltimore; T. R. Brown, Baltimore; L. Duncan Bulkley, New York; S. C. Busey, Washington; Louis A. Dühring, Philadelphia; C. Heitzman, New York;

1. Fox, G. H.: Photographic Illustrations of Skin Diseases, New York, E. B. Treat, 1880.

E. L. Keyes, New York; J. A. Octerlony, Louisville, Ky.; H. G. Piffard, New York; R. W. Taylor, New York; Arthur Van Harlingen, Philadelphia; F. D. Weisse, New York; James C. White, Boston, and Edward Wigglesworth Jr., Boston.

The meeting for organization met promptly at 6 o'clock on September 6. Dr. Wigglesworth, the chairman of the committee issuing the call, was continued in the chair, as was Dr. Bulkley as secretary pro tem., and Drs. Bulkley, Octerlony and Van Harlingen were appointed as a committee to prepare a constitution and by-laws and also to nominate the officers for the ensuing year. The next day, September 7, the constitution and by-laws were presented by the committee, and, after a thorough discussion, were amended and adopted, section by section. The American Dermatological Association was declared organized, and its first officers elected. They were as follows: president, James C. White; vice presidents, Louis A. Dühring and R. W. Taylor; secretary, L. Duncan Bulkley, and treasurer, James N. Hyde.

The Association then adjourned, to meet on the first Tuesday in September 1877 at Niagara Falls, N. Y.

So, without the trappings of royalty or all its fuss, feathers and fanfare, there was born painlessly and easily a lusty infant, appropriately enough at Old Penn, the center of activity for so many great men in American medicine. The infant has grown to manhood and now, at the age of 72, bears all the marks of a perpetually useful and happy life. The position of the American Dermatological Association is an enviable one. I shall present as briefly as possible the more important dermatologic contributions of the founders of the Association. The majority of them were men of extraordinary ability, tremendous enthusiasm and boundless energy. A few of them were leaders in American dermatology throughout their lives, and we will consider their careers more fully.

FOUNDERS OF THE ASSOCIATION

James Clarke White.—One of the outstanding pioneers in American dermatology, White was born on July 7, 1833. After a distinguished career as a student at America's oldest university, Harvard, from which he graduated in 1853, he spent a year abroad under the tutelage of that master dermatologist and brilliant teacher, Ferdinand Hebra. On his return to Boston in 1857 he took up general practice but never missed an opportunity to widen his dermatologic experience. In 1860 he opened a dispensary for cutaneous diseases. In 1863 he was appointed lecturer on diseases of the skin at the Harvard Medical School. The Massachusetts General Hospital created a department for diseases of the skin in 1870, and White was the logical choice for head of the department. He served this institution devotedly for thirty-three years. In 1871 he had the signal and deserved honor of being awarded the first

chair in dermatology to be established in the United States. Both of the aforementioned events marked a turning point in his career. He gave up his general practice and began the life work in which he was to accomplish so much. Between 1856 and 1913 White contributed to dermatologic literature approximately one hundred and twenty-five articles, fifty reviews, ninety-four editorials, twelve addresses and eight books and chapters. In June 1889 an article entitled "A Case of Keratosis (Ichthyosis) Follicularis"[2] appeared. White instead of Darier should have had the disease named after him, because Darier's

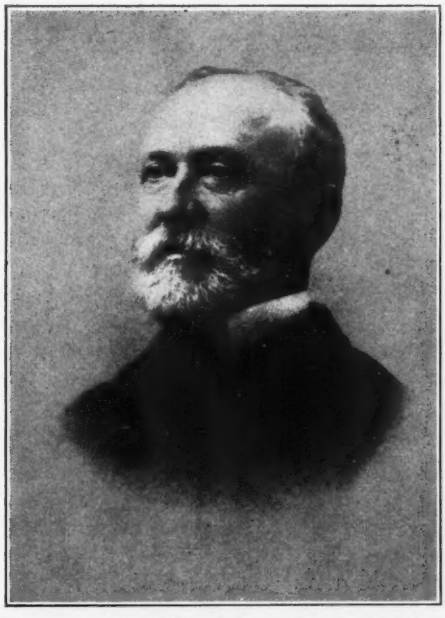


Fig. 1.—James Clarke White, M.D. (1833-1916).

article did not appear until a month later. On May 14, 1887, White published a 210 page book on dermatitis venenata, which work was the first presentation of this important subject in dermatologic literature.[3] He served as chairman of the section of dermatology and syphilology of the International Medical Congress held in Philadelphia from Sept. 4 to 9, 1876. He became the first president of the American Dermatological

2. White, J. C.: A Case of Keratosis (Ichthyosis) Follicularis, J. Cutan. & Genito-Urin. Dis. **7**:201 (June) 1889.

3. White, J. C.: Dermatitis Venenata: An Account of the Action of External Irritants on the Skin, Boston, Cupples & Hurd, 1887.

Association, in 1877, and twenty-one years later he was again elected president. In 1907 he was made president of the Sixth International Dermatological Congress, which was held in New York. White became a corresponding member of the French and Argentine dermatologic societies and an honorary member of the dermatologic societies of Italy, London, Vienna, Berlin and New York.

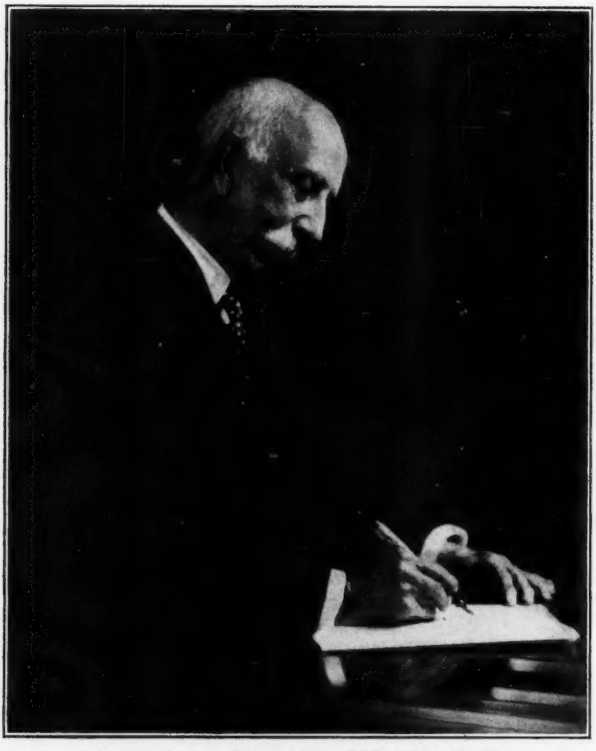


Fig. 2.—George Henry Fox, M.D. (1846-1937).

White was dignified in appearance and somewhat austere in manner, especially when conducting scientific sessions. In personal contacts he was courteous and pleasant. He had a full and busy life. He knew how to work and how to play. With abundant health, fame, a splendid family, ample means, a devoted wife and such hobbies as botany, natural history, porcelains and colonial furniture, he was indeed a happy man. He even lived long enough to witness the enormous progress of his beloved specialty.

George Henry Fox.—Fox received his bachelor of arts degree from the University of Rochester in 1867 and the degree of doctor of Medicine from the University of Pennsylvania in 1869. He succeeded Dühring in an internship at "Old Blockley" (Philadelphia Hospital) and was shown through that institution by his fellow intern, Arthur Van Harlingen; thus, by a strange coincidence, within the space of three years that hospital nurtured three men who were destined to accomplish much in American dermatology. When Fox's term of service expired he left for Europe for intensive dermatologic training. In Berlin he studied under Virchow, and in Vienna, under Hebra, Neumann, Schroetter and Stoerk. In Paris he was a pupil of Bazin, Hardy and Vidal, and in London, of Tilbury Fox and Jonathan Hutchinson. He worked assiduously under these great masters for three years. It was in Tilbury Fox's service at the University College Hospital that he first met a fellow countryman, from New York, Henry G. Piffard. The two men immediately became close friends, and they remained so until the death of Piffard, nearly forty years later.

Fox settled in New York in 1873, and in the same year he was elected to membership in the New York Dermatological Society, of which organization he was elected president four times. In 1876 he was one of the sixteen founders of the American Dermatological Association. During the year of its golden jubilee (1925-1926) he served as honorary president, receiving the gavel from his son, Howard Fox, the retiring president. Between the years 1875 and 1907 Fox served as professor of diseases of the skin at the Women's Medical College of the New York Infirmary; Starling Medical College, Columbus, Ohio; the New York Post-Graduate Medical School and Hospital, and the Columbia University College of Physicians and Surgeons, New York. He resigned from the last-mentioned institution years before the retiring age in order that George T. Jackson, his chief assistant, might serve as professor—an example of his usual generosity to his subordinates. From 1883 to 1913 Fox was attending dermatologist at the New York Skin and Cancer Hospital.

In 1879 Fox published his "Photographic Illustrations of Skin Diseases."[1] Other editions appeared in 1881 and 1885. His "Skin Diseases of Children" was published in 1897.[4] He described matchbox dermatitis in 1888, this description being probably the earliest report of contact dermatitis in the literature. In 1902, in collaboration with Fordyce, he reported a chronic, itching papular eruption of the axillas and pubes (Fox-Fordyce disease). He was elected president of the Medical Society of the County of New York in 1891 and of the Medical Society of the State of New York in 1894. In 1926 he published his

4. Fox, G. H.: Skin Diseases of Children, New York, W. Wood & Co., 1897.

"Reminiscences," [5] a delightful autobiography, every page of which evinces his extraordinary modesty. On the many occasions that we were together I never heard him speak of his own honors, but he was always ready to speak of those around him who had attained a high degree of proficiency in the specialty he so greatly loved. Another of Fox's most lovable traits was the extraordinary friendship and interest which he manifested for the young tyros of his specialty. His willingness to help them in every way possible was expressed without the

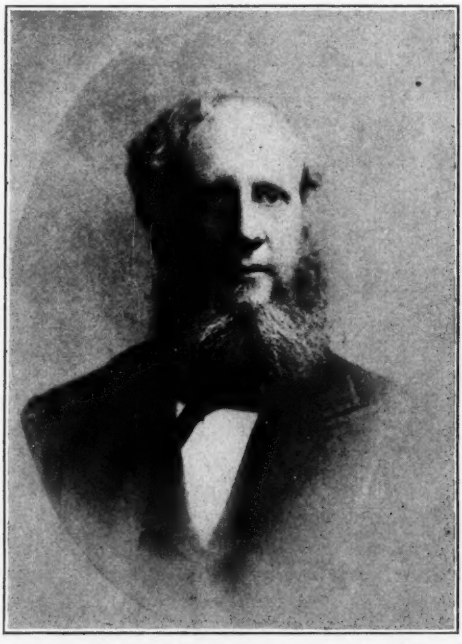


Fig. 3.—Louis Adolphus Dühring, M.D. (1845-1913).

slightest trace of condescension. As Pusey rightly stated, "He was perhaps the friend of more American dermatologists than any other one of his generation."

Louis Adolphus Dühring (1845-1913).—Dühring was a master in dermatology. After graduating from the University of Pennsylvania in 1867 and serving an internship in the Philadelphia Hospital, he went abroad and devoted himself assiduously to the study of dermatology in Vienna, under Hebra, and also in Berlin, London and Paris. His

5. Fox, G. H.: Reminiscences, New York, Medical Life Press, 1926.

vacation periods were spent in the study of leprosy in Constantinople and in Norway. He was one of the founders of the American Dermatological Association and twice its president. In 1877 he published the third American textbook on cutaneous diseases, which ran through three large editions.[6] He also brought out a chromolithographic atlas of cutaneous diseases [7] and projected an encyclopedic work, to be issued in parts, on diseases of the skin. The first part appeared in 1895 and the second in 1898, but the work was never completed.[8] Dühring was a prolific writer, a score of his articles being on the subject of dermatitis herpetiformis (Dühring's disease).

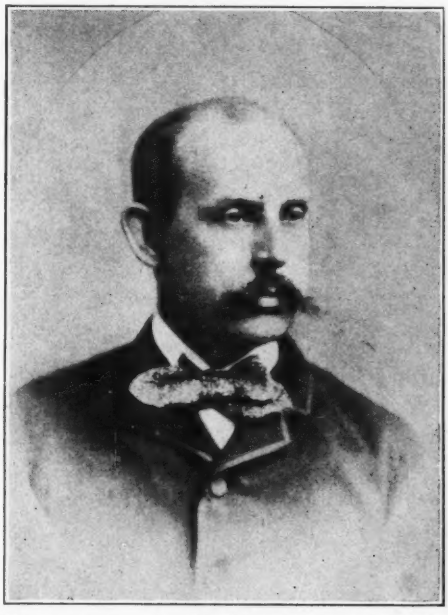


Fig. 4.—Arthur Van Harlingen, M.D. (1845-1936).

He soon received the appointment of clinical lecturer at the University of Pennsylvania; he then advanced to the position of clinical professor and later to that of full professor, a post which he filled with great honor from 1875 to 1910. Dühring was a great teacher and a

6. Dühring, L. A.: A Practical Treatise on Diseases of the Skin, Philadelphia, J. B. Lippincott & Co., 1877.

7. Dühring, L. A.: Atlas of Skin Diseases, Philadelphia, J. B. Lippincott & Co., 1876-1880, pts. 1-7.

8. Dühring, L. A.: Cutaneous Medicine: A Systematic Treatise of the Diseases of the Skin, Philadelphia, J. B. Lippincott Co., 1895, pt. 1; 1898, pt. 2.

clear, comprehensive and accurate writer. His descriptions of dermatitis herpetiformis are masterly in form and clarity. In his clinical work he was never satisfied until he had examined a completely stripped patient from head to foot. In his later years he became much less active and devoted much time to financial speculation. When he died, on May 8, 1913, he left, to every one's astonishment, more than a million dollars, which, after he had generously provided for relatives, he devoted to his alma mater, medical societies and charities. His most faithful associate was Arthur Van Harlingen, of Philadelphia.

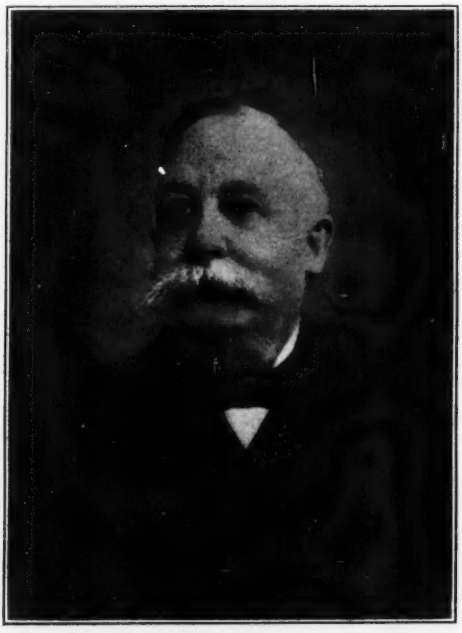


Fig. 5.—Robert W. Taylor, M.D. (1842-1908).

Arthur Van Harlingen (1845-1936).—Dühring's associate, Van Harlingen (1845-1936), of Philadelphia, was also a founder of the American Dermatological Association. He was a fellow intern of Dühring's at the Philadelphia Hospital in 1867 and assisted him in the dispensary and outpatient department of the University Hospital. He helped found the Philadelphia Polyclinic in 1885 and became its first professor of dermatology. He illustrated with pen and ink drawings the second edition of Dühring's "Treatise on Skin Diseases" and published a handbook on cutaneous diseases which ran through a number of

editions. This book contains tables of the differential diagnosis of the commoner dermatoses, which tables are of great practical value.[9]

Robert W. Taylor (1842-1908).—Taylor made important contributions to the study of syphilis. He made a noteworthy contribution to the subject with his book on syphilis of the bone[10] and also with his "Atlas."[11] Taylor was one of the organizers of both the New York Dermatological Society and the American Dermatological Association. He taught dermatology at the New York Post-Graduate Medical School and Hospital, succeeding George H. Fox as professor. In 1876 he described idiopathic cutaneous atrophy of the extremities.[12] Known to his intimates as "Bob" Taylor, he was a man of forceful opinions and a born fighter.

Henry Granger Piffard (1842-1910).—Piffard played an important role in the development of American dermatology. Through his brilliant, many-faceted mind, bordering on genius, he focused the attention of America, if not Europe, on his specialty, which during his early years was still in its infancy; its growth to lusty manhood was due in part to his devoted ministrations.

Piffard was born in Piffard, N. Y., on Sept. 10, 1842. He graduated from the University of the City of New York in 1862 and received his medical degree from the Columbia University College of Physicians and Surgeons in 1864. His interest in dermatology manifested itself soon after graduation. He left for Europe to perfect himself in the specialty and visited various medical centers but spent most of his time with Tilbury Fox at the latter's dermatologic clinic at the University College Hospital in London. It was there that his lifelong friend, George Henry Fox, first met him. The close friendship uniting them lasted until Piffard's death, nearly forty years later. The friendly association of these two men for nearly half a century can be readily understood by those fortunate enough to be familiar with them and to know how much they accomplished in establishing a firm foundation for the specialty they both loved, not only in the city of New York but in the world at large.

On his return from Europe, Piffard established himself in New York. He helped materially in the founding of the New York Dermatological

9. Van Harlingen, A.: Handbook of the Diagnosis and Treatment of Skin Diseases, Philadelphia, P. Blakiston Son & Co., 1884.

10. Taylor, R. W.: Syphilitic Lesions of the Osseous System in Infants and Young Children, New York, W. Wood & Co., 1875.

11. Taylor, R. W.: A Clinical Atlas of Venereal and Skin Diseases, Philadelphia, Lea Brothers & Co., 1889.

12. Taylor, R. W.: On a Rare Form of Idiopathic Localized or Partial Atrophy of the Skin, Arch. Dermat. **2**:114 (Jan.) 1876.

Society, on May 18, 1869. This medical body has the honor of being the oldest dermatologic society in the world. Piffard was also one of the organizers of the American Dermatological Association and later its president. In 1871 he became visiting dermatologist to the New York City Hospital (Welfare Island), the first institution in the United States to establish dermatologic wards. He served this institution until 1885, when he was appointed consulting dermatologist. He became professor of diseases of the skin in the medical department of New York University

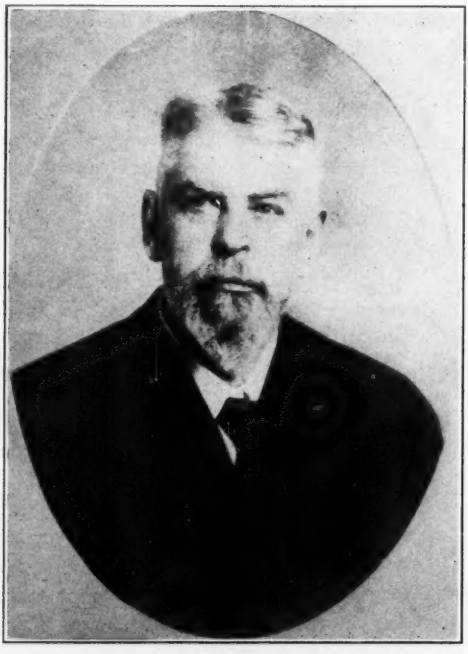


Fig. 6.—Henry Granger Piffard, M.D. (1842-1910).

and served this institution for many years. He was emeritus professor there at the time of his death.

Piffard wrote the second original textbook on diseases of the skin to be published in America,[13] but as early as 1868 he had translated Hardy's "The Darthrous Diathesis, or Eczema and its Allied Affections." In 1881 his "Treatise on the Materia Medica and Therapeutics of the Skin" first appeared.[14] According to Andrew R. Robinson, Piffard

13. Piffard, H. G.: An Elementary Treatise on Diseases of the Skin, for the Use of Students and Practitioners, New York, Macmillan & Co., 1876.

14. Piffard, H. G.: A Treatise on the Materia Medica and Therapeutics of the Skin, New York, W. Wood & Co., 1881.

deserves the credit for the first use of the term tuberculid, as he described this lesion in 1892, four years before Darier's work on the subject.

Piffard had a warm heart, and, though he was most combative at times, even to the point of eccentricity, he was a lover of peace and good will. As George Henry Fox aptly put it, he was "a blazing meteor in our dermatologic firmament."

Edward L. Keyes.—Keyes was born at Fort Moultrie, in Charleston Harbor, S. C., on Aug. 28, 1843. His father, an army officer who

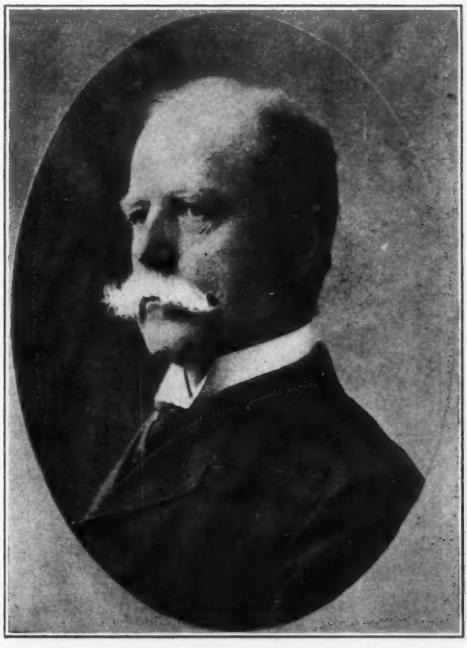


Fig. 7.—Edward L. Keyes, M.D. (1843-1924).

eventually became a Major General of the United States Army, was stationed there at the time. He received his bachelor of arts degree from Yale University in 1863 and the degree of Doctor of Medicine from New York University Medical College in 1866. On the advice of his preceptor, William H. Van Buren, he went abroad to specialize in dermatology. He was one of the founders of the New York Dermatological Society, in 1869, and of the American Dermatological Association, in 1876. In 1871 he was appointed lecturer in dermatology at Bellevue Hospital Medical College, and in 1881 he became professor of cutaneous and genitourinary diseases at the same school. He served

the New York City Hospital (Welfare Island) from 1870 to 1876 and one year later was appointed consultant.

Keyes was deeply interested in genitourinary surgery, but he made a number of valuable contributions to dermatologic literature. One of his greatest contributions was a paper on the effect of small doses of mercury on syphilitic blood, which work first appeared in January 1876.[15] This paper was incorporated in an essay on the same subject, which was read by Keyes before the section of dermatology and syphilology at the International Congress at Philadelphia in September 1876.

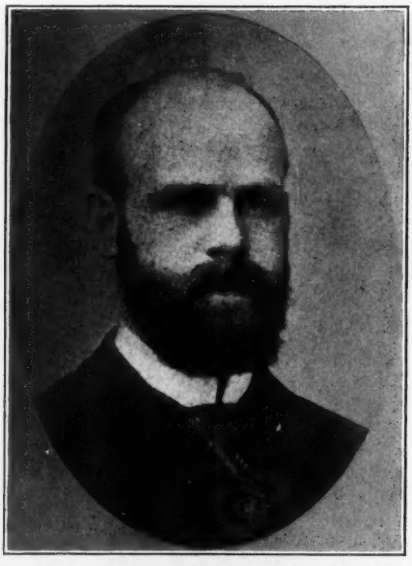


Fig. 8.—L. Duncan Bulkley, M.D. (1845-1928).

W. H. Van Buren and E. L. Keyes collaborated on a textbook on genitourinary diseases and syphilis, which remained a classic for many years.

L. Duncan Bulkley (1845-1928).—Bulkley received his medical degree from the Columbia University College of Physicians and Surgeons in 1869 and spent several years at the Hôpital Saint-Louis in Paris. On his return to New York he became most active in derma-

15. Keyes, E. L.: The Effect of Small Doses of Mercury in Modifying the Number of Red Blood Corpuscles in Syphilis: A Study of Blood-Counting with the Hematimetre, Am. J. M. Sc. **71**:17, 1876.

tology. He was one of the founders of the American Dermatological Association and its secretary at the first annual meeting, which was held at Niagara Falls, N. Y., on Sept. 4, 1877. Dr. Bulkley founded the New York Skin and Cancer Hospital on Jan. 1, 1883, and began a series of clinical lectures there in 1899. They became quite popular, and he kept them up until a few years before his death. He wrote several hundred articles and six or eight textbooks, mostly devoted to dermatotherapy, in which he had a deep interest. Bulkley was largely responsible for the formation of the Section on Dermatology and Syphilology

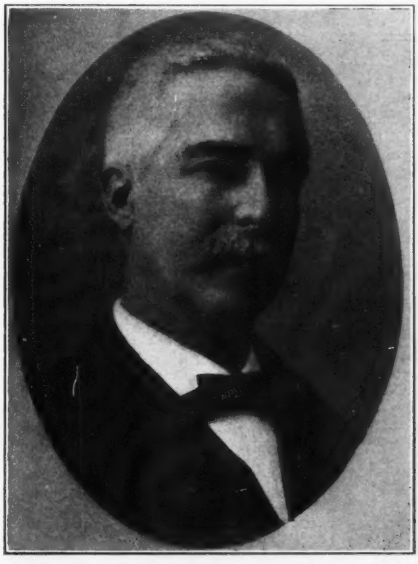


Fig. 9.—Edward Wigglesworth, M.D. (1840-1896).

of the American Medical Association, in Chicago in 1888, and he was chairman of its first meeting, on May 8, 1888, in Cincinnati.

Edward Wigglesworth (1840-1896).—Dr. Wigglesworth, of Boston, graduated from Harvard College in 1861 and from Harvard Medical School in 1865. He did five years of postgraduate work in Europe, and most of this time was devoted to dermatology. On his return to Boston he established at his own expense a free clinic for charity patients with diseases of the skin. This was discontinued when he joined the dermatologic staff of the City Hospital in 1877. He served as instructor in dermatology at the Harvard Medical School. Dr. Wigglesworth was independently wealthy. He had a large library on dermatology and a fine collection of moulages by Baretta, all of which

he donated to the Harvard Medical School. He was a founder of the Boston Medical Library and an active member of the Boston Dermatological Club. In his early professional life he contributed much of importance to the dermatologic literature of his time.

Faneuil D. Weisse (1842-1901).—Dr. Weisse was a student under Sir Erasmus Wilson and on his return to New York was the first lecturer on diseases of the skin at New York University, in 1865. In 1867 Dr. Weisse was appointed clinical professor. He resigned in 1874. He wrote little on dermatology but was greatly interested in it and was particularly gifted in stimulating the interest of his fellow

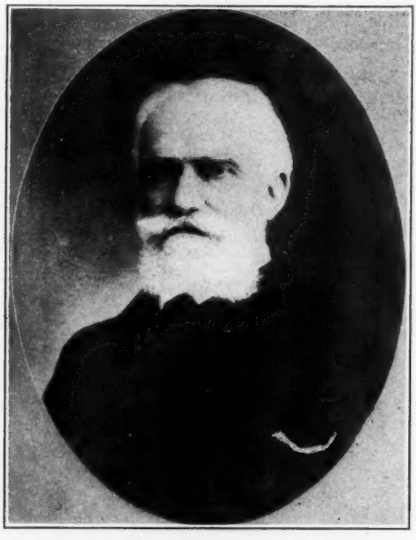


Fig. 10.—Faneuil D. Weisse, M.D. (1842-1901).

workers in the subject. Dr. Weisse conceived the idea of a dermatological society in America while studying his specialty abroad. This idea crystallized in the founding of the New York Dermatological Society on May 18, 1869, at the home of Henry D. Bulkley. The success of this society caused Dr. Weisse to consider the founding of a national dermatological society, and he helped to organize the American Dermatological Association. It is interesting to note that of the sixteen original founders of the American Dermatological Association, six were also founders of the New York Dermatological Society.

I. E. Atkinson (1846-1906).—He was very active in dermatology in Baltimore. A clinical professorship in that branch of medicine was

established by the University of Maryland in 1879, and Dr. Atkinson was the first incumbent. While he wrote a number of articles on dermatology, he was particularly interested in syphilis and wrote some important papers on that subject. Dr. George Henry Fox's appraisal of Atkinson follows: "His keen and clearly expressed views in all vexed questions added greatly to the interest of our discussions, while his power of careful observation may still be seen in the papers which he contributed."[16]

Other Founders.—Drs. L. P. Yandell Jr. and J. Octerlony, of Louisville, Ky., while founders of the Association, were, according to Dr. George H. Fox, never in close touch with it. Dr. Yandell was

Fig. 11.—I. E. Atkinson, M.D. (1846-1906).

the more active of the two men and attended the annual meetings of the Association more frequently than did Octerlony. Dr. White, in his address at the first meeting of the Association, credited Yandell with eight dermatologic articles written prior to 1877.[17] Dr. Yandell also served as the first lecturer on dermatology at the University of Louisville.

Dr. S. C. Busey of Washington, D. C., one of the organizers of the Association, graduated from the University of Pennsylvania in 1848

16. Fox, G. H.: The Founding of the American Dermatological Association, Arch. Dermat. & Syph. **14**:371 (Oct.) 1926.

17. White, J. C.: Dermatology in America, New York, G. P. Putnam's Sons, 1878.

and began medical practice in Washington in 1849. He was interested in general medicine and was a voluminous writer of medical articles, about one hundred and fifty in all, but wrote only one on a dermatologic subject, poison ivy dermatitis, which appeared in 1873. In his "Personal Reminiscences" of 373 pages, published in 1895, he did not mention the American Dermatologcial Association. Neither George H. Fox, Dühring, or Pusey mention him; there is a similar lack of reference to T. R. Brown of Baltimore.

Dr. Carl Heitzman (1836-1896) of New York practiced dermatology in Vienna and must have been closely associated with Hebra, for

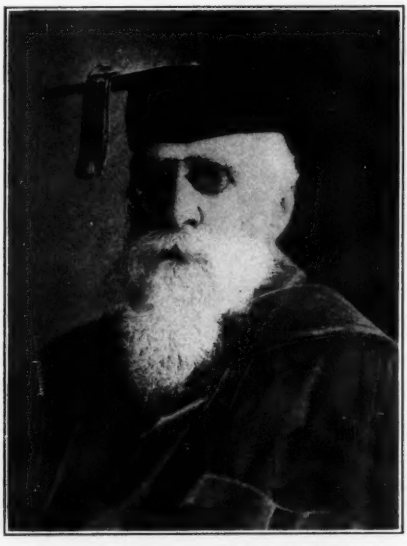


Fig. 12.—S. C. Busey, M.D. (1828-1901).

he painted many of the plates of Hebra's "Atlas" in 1864-1865. He later came to New York to practice and was recognized as an able dermatologist. He was present at the organization meeting of the Association and regularly attended its annual meetings, discussing many of the papers presented. He contributed some articles to the medical journals but was never invited to join the New York Dermatological Society and was most unpopular with his colleagues in New York city because of his lack of tact in criticizing their diagnoses and his assumption that European dermatology was infallible.

It is my opinion that, in all fairness, the sixteen men who successfully organized the American Dermatological Association should be classed as founders and that the thirteen who, according to the records,

did not attend either the preliminary or organization meeting, but joined before the first official meeting in 1877, should be known as charter members. These men were W. Brodie, A. Brooks, R. Campbell, H. T. Damon, W. H. Draper, D. W. Hand, W. A. Hardaway, J. N. Hyde, B. F. Jeffries, F. F. Maury, A. R. Robinson, C. G. Smith and R. F. Weir. (Of this number, only three attended the first meeting, in 1877. They were Drs. Brodie, Hyde and Campbell.) I feel so strongly about this point that I do not discuss the careers of the aforementioned thirteen men in this address, because I consider only those who attended the preliminary and organization meetings to be the real founders of the Association.

Fig. 13.—Carl Heitzman, M.D. (1836-1896).

FIRST MEETING OF THE AMERICAN DERMATOLOGICAL ASSOCIATION

The first meeting was held at the Cataract House on September 4, 5 and 6. Despite the fact that only fifteen of the original twenty-nine charter members attended, the meeting was not dampened in the least, as it proved a real success. In fact, it did not differ in any appreciable degree from the meetings of today. There was a council, instead of a board of directors. The places in the program were decided by lot. The council invited the foreign "notables" in dermatology at that time to attend the first meeting or present a paper. Of course no one came, and only Dr. Dyce Duckworth of London sent a paper. Letters were received from only twelve. One foreign dermatologist, Dr. Guntz of

Dresden, sent a congratulatory telegram. Reprints were received from five men. With this dubious blessing from Europe did the Association start its first year.

Dr. James C. White read his beautifully expressed and scholarly address on "Dermatology in America," which reviewed the progress of American dermatology from such pioneers as Henry D. Bulkley and Noah Worcester to 1877, at which time there were in the medical faculties of our medical schools four professors, at the University of Vermont and at Bellevue, Chicago and Harvard; five clinical professors, at New York University, the College of Physicians and Surgeons, Long Island College Hospital, the University of Pennsylvania and the Woman's Medical College of the New York Infirmary; six lecturers, at Missouri Medical College, Detroit Medical College, the University of Louisville, the College of Physicians and Surgeons of Baltimore, the Medical College of Ohio and Albany Medical College, and one instructor, at Jefferson Medical College. An American dermatologic journal had been published regularly since 1870. The New York Dermatological Society had been flourishing since 1869, the American Dermatological Association was taking her first steps at the age of one, three American textbooks in dermatology had been published, and many dermatologic clinics had been established. All this superlative progress had occurred in about eight years.

The immediate effect of Dr. White's paper was the appointment of a committee on statistics and on nomenclature. Eighteen papers were presented. A paper not accepted by the Association was read by a Dr. Brooks of Chicago, who was apparently an early American "gate crasher," as he was not a member of the Association. The title was "Acute Conditions of Disease Excited by Iodide of Potassium." The paper was entirely limited to an account of the internal manifestations of iodine sensitivity. I mention it only because Dr. Dühring in discussing it expressed regret that no mention had been made of the iododermas caused by small doses of the iodides. He reported the case of a patient who, after taking 10 drops of potassium iodide three times a day for one and a half days, acquired a severe bullous eruption which disappeared when the medication was discontinued. Some time later, the iodide was given again and the same eruption reappeared. This early record of sensitivity to small doses of iodine is of interest seventy years later because of the present role of iodized salt in occasionally producing similar lesions.

Dr. Bulkley's paper "On the Eczema Marginatum of Hebra, etc." was excellent, as he proved the presence of fungi in all the 10 patients. The remedy recommended was sulfurous acid, chemically pure and used

undiluted. Dr. Bulkley was still using it when I was his office associate nearly forty years later. Oddly enough, it is of great value in non-eczematized areas of infection.

Dr. Campbell's paper, "A Case of Prurigo of Hebra," brought out in the discussion the fact of its great rarity in America. A total of only 6 cases had been seen by the ten discussers.

Dr. Yandell's paper, "The Etiology of Cutaneous Diseases," was the poorest of the lot, as it was based on his claim that aside from diseases such as parasitic ones and syphilis, the large majority of acute diseases of the skin, such as eczema, urticaria and erythema, were caused by malaria, which statement was energetically condemned in the discussion by Drs. White, Bulkley, Atkinson and even Heitzman. It would take too long to describe all the papers, but taken all in all they were surprisingly good, considering the fact that they represented views in dermatology now seventy years old. At this first meeting of the Association such brilliant dermatologists as Dühring, Fox, Hyde, Taylor and White met for the first time in dermatologic debate, and the result was in itself an event of great significance in the development of dermatology in America.

EPILOGUE

May I, in conclusion, quote the last paragraph of Dr. James C. White's presidential address at the first meeting? It is as true today as it was seventy-one years ago. In speaking of the Association, Dr. White said: "Its formation may be regarded as the happy culmination of progress in a national dermatology of which we may well be proud. Let us cherish it warmly, serve it willingly and always, and make its future as sure as its present promise is tonight."

The American Dermatological Association has, in its development in the past seventy-one years, amply fulfilled Dr. White's prediction and in my opinion has served as a monument to its founders. I feel confident that it will continue its progress in the hands of the successors of the present members and that they will carry it on to increased glory. However, if they have not found the actual etiologic factors and a specific for some members of that rather large group of dermatologic ills headed by psoriasis and chronic lichenoid dermatitis, I shall come back to earth and tweak their ears, God bless them.

1364 North Avenue (3).

DIAGNOSIS AND TREATMENT OF PIGMENTED NEVI

Consideration of Some of the Pitfalls

S. WILLIAM BECKER, M.D.
CHICAGO

THERE is still considerable difference of opinion between dermatologists, on the one hand, and surgeons and oncologists, on the other, relative to the treatment of pigmented nevi, or "moles," as they are commonly called. The dermatologist's aid is enlisted more frequently for the cosmetic treatment; less frequently is his opinion sought relative to the significance of a lesion which has enlarged, has ulcerated or has become darker. Thousands of pigmented moles are treated daily for purely cosmetic reasons, with results that are permanently satisfactory to the patient. The surgeon and the oncologist, on the other hand, are consulted most frequently for the treatment of tumors which have supposedly originated in pigmented moles and which have not responded to therapeutic measures carried out by the general practitioner or, perhaps occasionally, by the dermatologist.

The criteria for the diagnosis of a pigmented nevus include primarily the presence of nevus cells. A nevus cell may be considered as a cell which has arisen by benign proliferation of melanoblasts or potential melanoblasts. For this reason, blue nevi are also included. The so-called intraepidermal nevus does not belong in this group because previous studies [1] have shown that, even though the tumors may contain much melanin and may even be black, they do not contain nevus cells and have been derived by benign proliferation of true epidermal cells.

DERMATOLOGIC TREATMENT OF PIGMENTED NEVI

Ormsby and Montgomery [2] stated that ordinary pigmented nevi are treated for cosmetic reasons by electrolysis, application of solid carbon dioxide, diathermy or cautery. They recommended deep removal of

From the Section of Dermatology, the School of Medicine, University of Chicago.

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, on June 4, 1947.

1. Becker, S. W.: Benign Epidermal Neoplasms, Arch. Dermat. & Syph. **26**:838 (Nov.) 1932.

2. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

nevi, especially the flat, or junction, type, when they occur on the soles, at the belt line or in other areas subject to trauma. They also advocated wide excision of any nevus that is showing signs of increased growth or increase in pigmentation. They emphasized that treatment should be complete because of the danger of the formation of a melanoma in an incompletely removed nevus. They deprecated the electrolytic removal of hairs from a hairy nevus without complete treatment of the entire lesion.

MacKee and Cipollaro [3] made the following statement:

> The common mole may be handled satisfactorily with electrolysis with little if any permanent defect. Dermatologists have been employing this method for thirty or more years and there has not been a single instance of cancer. One must be certain of the diagnosis, however. It is unwise to treat a cerebriform nevus by any method that fails to remove every abnormal cell.

They also recommended the use of solid carbon dioxide and electrodesiccation. They expressed the belief that blue-black nevi should be excised when they are in sites where they are likely to be traumatized or irritated or when they exhibit any evidence of activity, such as increase in size, crusting or ulceration.

Sutton and Sutton [4] stated that destruction should be complete and include normal tissue beyond the periphery and depth of nevus tissue.

Andrews [5] stated that it is usually best not to treat macular nevi, even though they are objectionable cosmetically. He advised clipping small, fleshy, pedunculated moles at the base and the removal of large lesions by a scalpel, with local anesthesia. Small, soft hairy moles are treated by electrolysis, both for removal of hair and for destruction of the lesion itself. In case such a lesion exhibits fissuring, crusting or bleeding or enlarges or shows increase in pigmentation, it should be excised. If it becomes infected, it is treated with wet dressings, and after the inflammation has subsided it is excised surgically. Andrews suggested radical surgical excision for black, bluish black or brownish black, flat or rounded moles, especially when there is an increase in extent or depth of pigmentation. Brownish, silghtly elevated, nummular or larger moles are excised in toto or piecemeal, with subsequent skin grafting if it is advisable. Andrews also recommended electrosurgery, the use of solid carbon dioxide, actual cautery and other methods as satisfactory in some instances. He expressed the belief that radium and roentgen rays are unsatisfactory means of therapy.

---

3. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, New York, American Journal of Cancer, 1938.

4. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

5. Andrews, G. C.: Diseases of the Skin for Practitioners and Students, ed. 3, Philadelphia, W. B. Saunders Company, 1946.

Klauder,[6] and also Traub,[7] discussed the dermatologic treatment of pigmented nevi.

SURGICAL TREATMENT OF PIGMENTED NEVI

Pack and Livingston [8] stated:

Although electrocautery or electrodesiccation, using either the bipolar or monopolar currents, is eminently satisfactory for removal of some pigmented lesions of the skin, notably the epithelial papillomas, there is an element of danger in removing the true mole, i e., that which contains neval cells, by this technic, unless the operator is radical in the cauterization. Perhaps thousands of such true nevi are treated by dermatologists without mishap for every one that recurs as malignant melanoma, but the sequence of malignant transformation of an

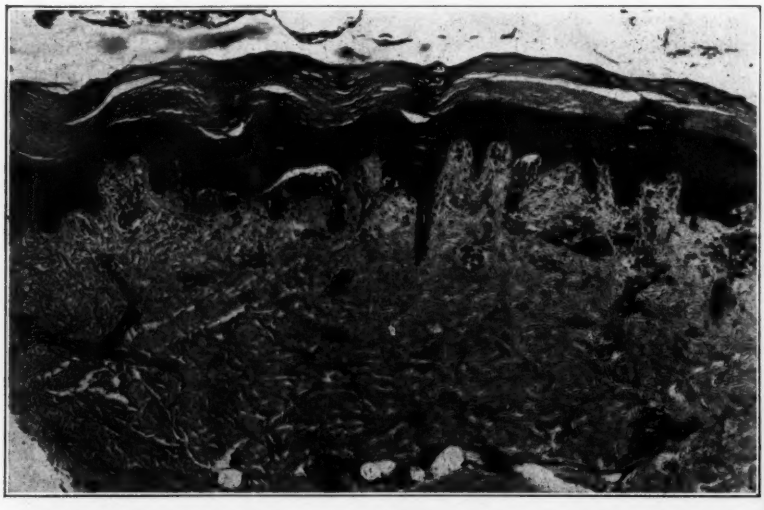


Fig. 1.—Cellular nevus of the sole, type A and B. Nevus cells are intimately associated with the epidermis and are present in groups in the superficial dermis. Low power lens; hemalum, erythrosin and saffron stain.

apparently quiet nevus following incomplete electrodesiccation has occurred with unpleasant frequency in the case histories at our disposal.

They further stated that the proper treatment of a benign nevus is complete surgical excision, with the use of either a scalpel or an endotherm cutting current. They expressed the belief that large pigmented

6. Klauder, J. V.: Treatment of Nevi: The Hazard of Insufficient Destruction of Pigmented Nevi, Pennsylvania M. J. **33**:472, 1930.

7. Traub, E. F.: The Treatment of Nevi, Clinics **3**:974, 1944.

8. Pack, G. T., and Livingston, E. M.: The Treatment of Pigmented Nevi and Melanomas, in The Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, vol. 3, chap. 122, pp. 2071-2094.

nevi may be safely removed by serial operation before puberty, but that the influence of trauma may change the character of the tumor after adolescence.

Wood [9] made the following observation relative to melanoma:

> Many surgeons, however, believe that the chief hope in reducing the mortality of this most fatal type of neoplasm must be placed in prophylactic treatment; that is, the prompt removal of pigmented moles in all cases in which the anatomic locality renders them liable to irritation or injury.

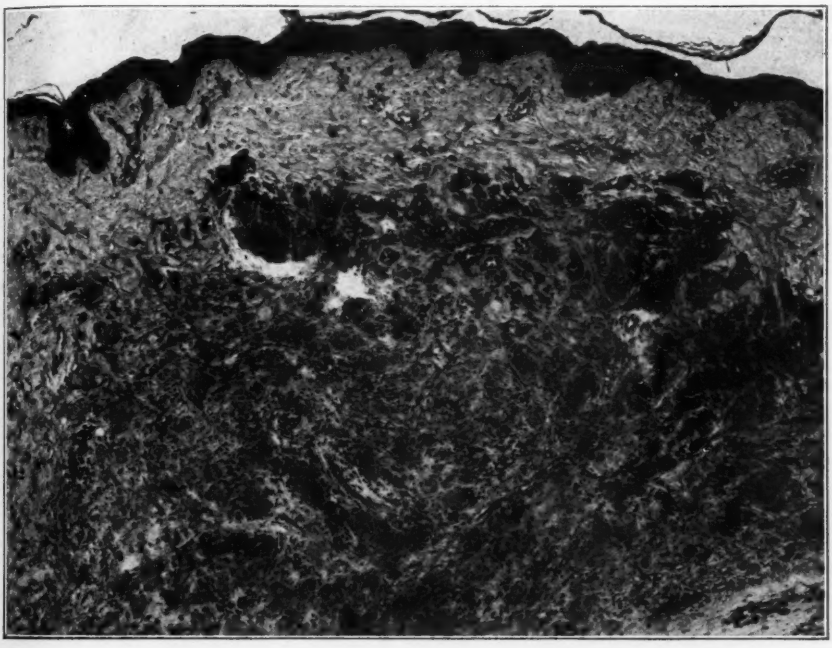


Fig. 2.—Nerve nevus, type B and C. Nevus cells are present in groups and strands in the dermis, separated from the epidermis by a broad band of collagen. In the deeper portions, *lames foliacées* are present, and the nevus is less cellular. Low power lens; hemalum, erythrosin and saffron stain.

MICROSCOPIC CLASSIFICATION OF NEVI

As I have previously reported,[10] nevi vary from the purely cellular type, which consists of nevus cells which are definitely attached to the

9. Wood, F. C.: Tumors, in Nelson Loose-Leaf Surgery, New York, Thos. Nelson & Sons, 1941, vol. 2, p. 65.

10. Becker, S. W.: Origin and Nature of Pigmented Nevi (Schwannomas), Arch. Dermat. & Syph. **30**:779 (Dec.) 1934.

epidermis and/or are arranged in groups and strands in the superficial dermis (fig. 1) to tumors which exhibit elongated cells with small nuclei and abundant protoplasm, predominantly in the deeper dermis. Such cells are at times arranged partially in the form of the *lames foliacées* of Masson, which resemble the corpuscles of Wagner and Meissner. The tumors which present a considerable percentage of the latter structure are known as "nerve nevi" (fig. 2). The transition from the cellular to the nervelike structures is gradual and imperceptible, as stated by Miescher and von Albertini.[11] The latter authors classified nevi into three types, as follows:

Type A. Epidermal segregation, with groups and cords of cells.
Type B. Infiltrative growth, exclusively intradermal.
Type C. Neurofibromatous structure, resembling Recklinghausen's neurofibroma.

Fig. 3.—Section from the periphery to the center of a nevus removed from the calf of the leg. In the periphery, only epidermal islands of nevus cells are present (type A); nearer the center, dermal islands of cells are also seen (type A and B), and in the center, in addition to islands in the epidermis and dermis, elongated cells are situated more deeply (types A, B and C). Low power lens; hematoxylin and eosin stain.

They presented their data concerning 100 nevi, as shown in table 1.

TABLE 1.—*Microscopic Classification of 100 Nevi (Miescher and von Albertini*[11])

Type of Nevus	Number of Cases
A	4
B	2
C	0
A and B	85
A and C	2
A, B and C	7

11. Miescher, G., and von Albertini, A.: Histologie de 100 cas de naevi pigmentaires d'après les méthodes de Masson, Bull. Soc. franç. de dermat. et syph. **42**:1265, 1935.

MATERIAL

I have recently studied 741 specimens removed from 681 patients on which the microscopic diagnosis of pigmented nevus had been made during the period from October 1927 into 1947, in the dermatologic laboratory of the School of Medicine of the University of Chicago. Most of the sections were stained by a trichrome method of Masson. After endeavoring to fit the lesions into the classification of Miescher and von Albertini,[11] I adopted a slightly different classification, as follows:

Type A. Lesions in which nevus cells are still definitely attached to, or actually integrated into, the epidermis.

Type B. Lesions in which no nevus cells are definitely attached to the epidermis but in which they are present in the dermis.

Type C. Nerve nevus type of Masson, some portions of which resemble neurofibroma.

Microscopic classification of the 741 lesions is given in table 2.

TABLE 2.—*Microscopic Classification of Nevi*

Type of Nevus	Percentage of Cases	Number of Cases
A	2.1	16
A and B	8.7	65
B	16.4	122
B and C	64.3	477
A, B and C	6.6	49
C	1.6	12
Total	100.0	741

It should be kept in mind that few tumors were studied by serial sections; hence diagnosis was usually made from a single slide, on which there were one to three or four adjacent sections. Miescher, in his article on nevi in Jadassohn's "Handbuch," called attention to the fact that the *Abtropfung* of Unna occurs slowly and in only a few areas in nevi, so that it may be missed if only a few sections are examined. Some of the sections did not extend deeply enough to include the entire tumor, so that evaluation of the deeper portion was inaccurate and incomplete. One section, which represented an entire tumor, showed type A alone at the end, types A and B a little nearer the center and type A with types B and C in the center. Hence the area which is sectioned makes considerable difference in the classification. Figure 4 shows a soft, fibrous tumor, with nevus cells in only one part.

The three criteria were difficult to apply. The first involved a decision as to whether or not nevus cells were actually attached to, or integrated with, the epidermis. This judgment was especially difficult

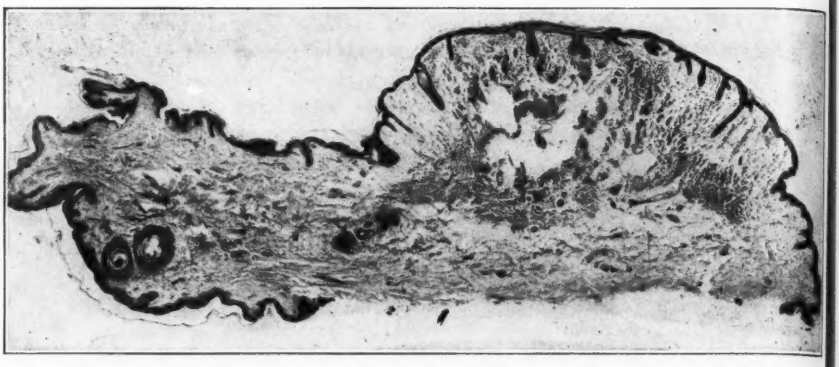


Fig. 4.—Soft, fibrous tumor. The portion on the left is identical with fibroma molle; that on the right shows a type B and C nevus, with groups and strands of cells superficially and elongated cells, resembling Schwann cells, in the deeper portion. Low power lens; hematoxylin and eosin stain.

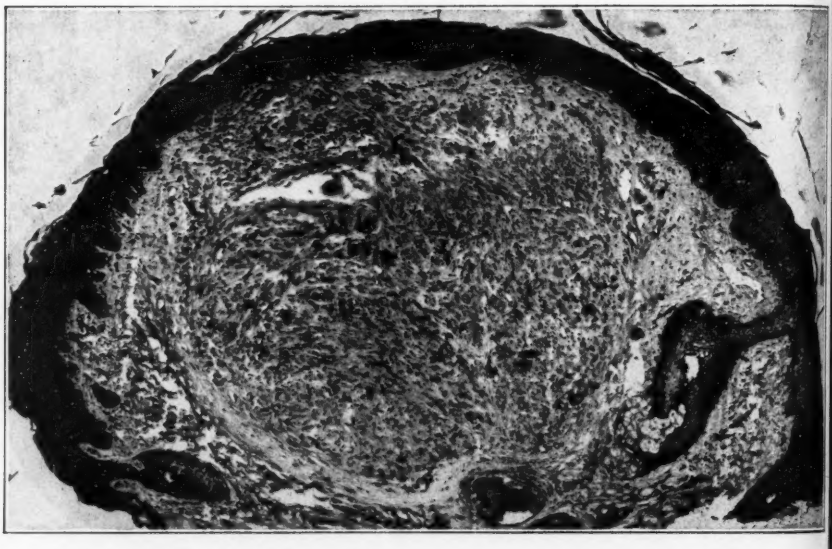


Fig. 5.—Nonpigmented nevus (?) removed from the brow. The entire tumor is composed of cells resembling Schwann cells, which fact would justify a diagnosis of type C nevus or neurofibroma (schwannoma). Low power lens; hemalum, erythrosin and saffron stain.

in the case of elevated tumors, in which the epidermis had been so compressed by nevus cells from within that such cells were often contiguous to the epidermis, but perhaps not definitely attached.

The second difficulty was encountered in determining whether the deeper portion of the nevus cell infiltration was of type C. When the *lames foliacées* (fig. 2) were pronounced, as they were in 50 instances, the decision was facilitated, but otherwise the gradual elongation of the nevus cells in the deeper locations made the decision difficult.

The third problem which introduced difficulties was the determination whether certain lesions should be classified as a type C nevus or as a neurofibroma. Such a lesion was illustrated clinically and microscopically by Traub and Keil.[12] The tumor was located near the eyebrow and was clinically a typical nonpigmented nevus. Microscopically, Satenstein had made a diagnosis of neurofibroma. I encoun-

TABLE 3.—*Distribution of 741 Nevi*

Area of Occurrence	Percentage of Cases	Number of Cases
Scalp	2.00	15
Face	40.76	302
Neck	10.37	77
Trunk	26.85	199
Upper extremities	4.45	33
Lower extremities	6.61	49
Genitalia	0.54	4
Location unknown	8.36	62

tered 12 such cases (fig. 5), in which a diagnosis either of neurofibroma or of type C nevus could be made with equal justification.

DISTRIBUTION OF NEVI

The anatomic distribution of the lesions on which microscopic examination of the nevus was made is given in table 3. This regional classification is not entirely accurate for the population at large, since many nevi which were removed for cosmetic reasons were located in exposed regions; hence in this series there is a predominance of lesions on the face and neck.

CLINICAL DIAGNOSIS OF PIGMENTED NEVI

Clinical diagnosis of the pigmented nevus is given in textbooks on dermatology and will not be considered here. Such a diagnosis was made for 710 lesions by experienced dermatologists and by graduate

12. Traub, E. F., and Keil, H.: The "Common Mole": Its Clinicopathologic Relations and the Question of Malignant Degeneration, Arch. Dermat. & Syph. **41**:214 (Feb.) 1940.

students in various stages of training, and a few specimens were sent to the laboratory by nondermatologic practitioners. The laboratory diagnoses of the 710 specimens are shown in table 4. Diagnosis was correct in 80 per cent of cases. Thirty-nine specimens proved to be seborrheic keratoses. In some of its forms, the so-called seborrheic keratosis, which I believe is a benign epidermal neoplasm,[1] appears

TABLE 4.—*Laboratory Diagnoses of 710 Lesions Diagnosed Clinically as Nevi*

Diagnosis	No. of Cases	Diagnosis	No. of Cases
Nevus	567 (80%)	Lentigo maligna with melanoma	1
Seborrheic keratosis	39	Condyloma acuminatum	1
Papilloepithelioma	20	Xanthoma	1
Carcinoma	17	Nevus sebaceus	1
Verruca vulgaris	10	Angiofibroma	1
Chronic inflammatory lesion	7	Pseudoxanthoma elasticum	1
Fibroma molle	6	Hemangioma with hemorrhage and thrombosis	1
Lentigo maligna	5	Duct of mucous gland	1
Fibroma	3	Sarcoid	1
Neurofibroma	2	Keratosis senilis	1
Lentigo	2	Lymphangioma	1
Melanoma	2	Melanosis	1
Adenoma sebaceum	2	Leukemid	1
Senile elastosis	2	No diagnosis made	9
Fibroxanthoma	2		
Melanosis	2		

TABLE 5.—*Clinical Diagnoses of 649 Lesions Diagnosed Microscopically as Nevi*

Diagnosis	No. of Cases	Diagnosis	No. of Cases
Nevus	567 (87%)	Melanoma	3
Seborrheic keratosis	15	Accessory nipple	1
Carcinoma	14	Xanthoma	1
Fibroma molle	9	Keratosis follicularis	1
Verruca vulgaris	7	Hemangioma	1
Lentigo maligna	6	Epithelioma adenoides cysticum	1
Papilloepithelioma	6	Granuloma pyogenicum	1
Adenoma sebaceum	5	Actinodermatitis	1
Cyst	5	Fibroangioma (mouth)	1
Fibroma	4		

identical with certain elevated pigmented nevi. It has its onset, however, later in life. Twenty specimens showed papilloepithelioma, also a benign neoplasm in which both the epidermis and the dermis participate. This lesion also appears later in life than does the pigmented nevus.

The clinical diagnosis was recorded for 649 lesions on which the laboratory diagnosis of pigmented nevus was made, as shown in table 5. The diagnosis was correct in 87 per cent of cases. In this instance, also, seborrheic keratosis was oftenest confused with the pigmented nevus.

The type of carcinoma which is mistaken for a nonpigmented nevus usually appears in the form of the semiglobular, smooth tumors of the face which show pseudocystic cellular infiltration microscopically.

CLINICAL DIAGNOSIS OF BLUE NEVUS

Although blue nevi were included in the series of pigmented nevi, they present diagnostic problems peculiar to themselves. A clinical diagnosis of blue nevus was made in 12 instances. The laboratory diagnoses on these specimens are given in table 6. Of the entire group of 741 nevi, a microscopic diagnosis of blue nevus was made on 22. The clinical diagnoses on these specimens are given in table 7. The

TABLE 6.—*Laboratory Diagnoses of 12 Lesions Diagnosed Clinically as Blue Nevi*

Diagnosis	Number of Cases
Blue nevus	6
No nevus found	2
Melanoma	1
Hemosiderotic histiocytoma	1
Tattoo	1
Syringocystadenoma	1

TABLE 7.—*Clinical Diagnosis of 22 Lesions Diagnosed Microscopically as Blue Nevi*

Diagnosis	Number of Cases
Blue nevus	6
Nevus pigmentosus	3
Melanoma	2
Fibroxanthoma	1
Diagnosis not made	10

number of cases in which a clinical or microscopic diagnosis of blue nevus was made is too small to warrant any conclusions.

COMBINATION OF NEVUS PIGMENTOSUS AND BLUE NEVUS

In addition to the 22 diagnoses of blue nevus just mentioned, a combination of the blue nevus and the ordinary pigmented nevus was noted in 6 cases. This observation, also mentioned by Montgomery and Kahler,[13] is important because the presence of melanoblastic cells in the depth of a nevus has led to the erroneous diagnosis of malignant melanoma arising in a pigmented nevus.

13. Montgomery, H., and Kahler, J. E.: The Blue Nevus (Jadassohn-Tièche): Its Distinction from Ordinary Moles and Malignant Melanomas, Am. J. Cancer **36**:527, 1939.

INFECTED NEVI

Fifteen specimens showed definite evidence of acute or chronic infection. This finding is important because of the enlargement of the lesions, a feature which sometimes causes patients to seek medical attention. In none of the specimens was there evidence of malignant proliferation, a process which has been said to follow infection.

AUTHOR'S TREATMENT OF PIGMENTED NEVI

After clinical and microscopic study of nevi, lentigo maligna and melanoma, I have adopted methods of treatment, by no means original, which I believe are safe and efficacious. Use of such methods will lessen subsequent melanoma formation in treated lesions to an irreducible minimum. The *sine qua non* for treatment is to determine whether the lesion is clinically a pigmented nevus, and not lentigo maligna or melanoma. History reveals that most nevi have been present since the patient can remember. In rare instances, acquired nevi, apparently harmless, have appeared later in the cases reported by Ebert [14] and by Arnold [15] at the ages of 11 and 28, respectively. A very few lesions in my series appeared in adult life. Nevus-like lesions appearing after infancy must be studied very carefully and observed closely before being considered harmless nevi. A recently appearing single brown lesion is usually lentigo maligna, which constitutes the early stage of malignant melanoma. Such a lesion should be excised surgically for biopsy. Nevi which have enlarged, have become ulcerated or have darkened should also be treated by surgical excision. The blue-black lesion is already a malignant melanoma and should be treated as such. Treatment varies slightly with the variety of nevus; hence each type will be discussed separately.

Macular Nevus.—This variety usually shows the A or the A and B types of configuration microscopically, so that destruction of the epithelium and cells at the epidermodermal junction suffices. With the use of local anesthesia, small lesions are cauterized with a major electrocautery deeply enough to destroy the epidermis and adjacent cells but not so deep as to cause appreciable scarring. There is no reason that solid carbon dioxide or electrocoagulation could not be used by one who is experienced in their use. The cosmetic result following cauterization is acceptable to the patient. Large macular nevi are treated by fulguration, with local anesthesia.

---

14. Ebert, M. H.: Multiple Pigmented Nevi: A Study of the Origin of the Nevus Cell, Arch. Dermat. & Syph. **37**:1 (Jan.) 1938.

15. Arnold, H. L., Jr.: Multiple Pigmented Nevi: Report of a Case, Arch. Dermat. & Syph. **40**:387 (Sept.) 1939.

Papular Nevus.—The microscopic picture of a papular nevus is usually that of type B or of types B and C. There may, of course, in some instances be epidermal nests of nevus cells, so that the microscopic designation becomes types A and B or types A, B and C. In the treatment of papular nevi on the face or neck, in order to determine whether intraepidermal nevus cells are present, one snips off with scissors the most superficial portion of the lesion for subsequent biopsy. The area is then cauterized with the electrocautery to such a depth that when the wound is healed the scar will be flush with the epidermal surface. In regions other than the face and neck, the entire papule is often removed by a cutaneous punch. No effort is made to destroy all dermal nevus cells, since, in my experience, they are harmless. It is my belief that removal of specimens for biopsy is entirely safe if the physician is prepared to carry out further measures within a week or so. I believe that the old idea that the removal of tissue for biopsy encourages the metastasis of malignant lesions is fallacious. The inflammatory reaction following the removal of tissue for biopsy seals the local lymphatics and temporarily discourages, rather than encourages, dissemination. If biopsy had been made of lesions later shown to be malignant, such malignant change could have been determined by an experienced dermatopathologist sufficiently early to improve the prognosis greatly. If such biopsy reveals any suspicion of abnormal growth, the area is subjected to wide surgical excision.

Hairy Nevus.—Small papular pilose nevi may be treated in two ways. First, a specimen from the lesion may be taken for biopsy and the lesion cauterized at the initial visit with subsequent removal of the hairs by the epilating needle. Or, second, the hairs may first be removed by the epilating needle, a specimen for biopsy taken from the mole and the mole cauterized at the first visit. Either method gives a satisfactory result. Removal of hair with the epilating needle without subsequent immediate treatment of the nevus is not considered safe.

Somewhat larger hairy nevi may be treated in infancy by application of solid carbon dioxide or another destructive method. After puberty, large hairy nevi may be treated by surgical excision and skin grafting. However, one should not lose sight of the admonition of Pack and Livingston [8] that such lesions should be removed before adolescence.

Pedunculated Nevus.—The treatment of a pedunculated nevus is simple and consists merely of clipping off the lesion at the base and cauterizing the base. This procedure removes the entire lesion, with the possible exception of a few deep nevus cells, which, in my experience, are harmless. A biopsy is made of all such specimens, and surgical excision of the area is carried out if there is any suspicion of malignancy.

Extensive Nevus.—In the therapy of extensive nevi, especially after puberty, the patient should be warned that continuous observation is vital because of the possibility of stimulation of melanoblasts to malignant proliferation. The two methods of choice are fulguration and excision, the latter to be followed by skin grafting.

Blue Nevus.—Because of their depth, the only logical treatment of blue nevi is surgical excision.

PROGNOSIS

The results of treatment of the common mole, which is papular or pedunculated, are excellent. In some instances, in which the brown color persists after initial cautery, a second treatment is given. The same procedure is followed if the resultant scar remains elevated above the level of the skin. The final scars are insignificant and are accepted by the patient. If any tendency to neoplastic proliferation is discovered in the biopsy of the elevated lesions, surgical removal of the area is called for. Such a surgical procedure results in an insignificant linear scar. Keloidal or hypertrophic scars following fulguration may be softened by filtered roentgen rays.

PITFALLS IN THE TREATMENT OF PIGMENTED NEVI

MacKee and Cipollaro[3] emphasized the prerequisite of accurate diagnosis before a lesion is treated as a nevus. Traub and Keil[12] called attention to the discrepancy, also reflected in my own series, between the clinical and the microscopic diagnosis. It seems that the diagnosis of "mole," or pigmented nevus, has been made too freely, especially by nondermatologic practitioners, and perhaps by dermatologists, without careful anamnestic study and biopsy.

Before a clinical diagnosis of nevus can be accurately made, a careful history should elicit the fact that the lesion has been present since early childhood. Any lesion which has appeared later should always be considered potentially dangerous and a biopsy made. It would seem that in practically all instances in which melanoma has followed treatment of a "mole" biopsy of the lesion at the time of treatment would have demonstrated cause for suspicion. In cases of frank melanoma, my efforts to obtain microscopic reports on supposed "moles" which had been previously removed have usually been unavailing. In some instances, in which such sections have been obtained, I have discovered that the initial lesion had already been a melanoma. Hence, it would seem to behoove one to make a biopsy of all elevated lesions diagnosed as pigmented nevi at the time of treatment.

Aside from cosmetic considerations, nevi are treated because of their potential malignant properties. Since, in my experience and in that of Satenstein,[16] Montgomery and Kernohan[17] and others, melanoma originates at the junction of the epidermis and the dermis, in cells that are intimately attached to the epidermis, the nevi which are of type A or combinations of type A are of greatest importance. Driver and MacVicar[18] advised removal of junction nevi as a diagnostic measure and for prophylaxis against the formation of melanoma. The maximum number of such lesions in my series was 130, forming about 17 per cent of the total. The actual number may be considerably less than this figure, because lesions were included in which nevus cells were contiguous, but may not have been intimately associated with the epidermis.

The large majority of lesions, namely, type B and the combination of types B and C, which constituted 599 specimens (81 per cent), are apparently harmless, although Ewing and Montgomery and Kernohan[17] stated that they had observed melanoma arising in dermal nevus cells. This group seems to verify numerically the contention of Traub and Keil[12] that the designation "common mole" should be applied to those lesions characterized histologically by intradermal collections of nevus cells. I can also confirm their opinion that such a lesion in its pure form, i. e., the type B and the type B and C varieties, rarely, if ever, becomes malignant.

The following cases illustrate some of the danger signs which are encountered in the diagnosis and treatment of nevi.

REPORT OF CASES

CASE 1.[19]—H. B., a girl aged 18, presented a brown macule, 8 mm. in diameter, on the shin, which growth, she stated, had been present for eight months. There had been no subjective symptoms. The lesion was removed locally for biopsy.

Microscopic examination (fig. 6) revealed that masses of melanoblastic cells, resembling nevus cells, had formed at the junction of the epidermis and dermis and were penetrating into the dermis and had penetrated into the epidermis. The latter feature led to the diagnosis of lentigo maligna, which has also been called a junction nevus. Since lentigo maligna is considered an early malignant melanoma, the area was widely excised surgically.

CASE 2.—N. M., a girl aged 16, had always had a small pigmented mole on her shoulder. It had occasionally become tender because of irritation by a shoulder

16. Satenstein, cited by Traub and Keil.[12]

17. Montgomery, H., and Kernohan, J. W.: Pigmented Nevi, with Special Studies Regarding a Possible Neuro-Epithelial Origin of the Nevus Cell, J. Invest. Dermat. **3**:465, 1940.

18. Driver, J. R., and MacVicar, D. M.: Cutaneous Melanomas: A Clinical Study of Sixty Cases, J. A. M. A. **121**:413 (Feb. 6) 1943.

19. Becker, S. W.: Pigmentary Diseases of the Skin, Clinics **3**:886, 1944.

strap, and it had been growing slowly. The patient presented a slightly elevated brown papule, 3.0 by 5.0 mm. in area. The lesion was completely removed locally.

Microscopic examination (fig. 7) showed a superficial nevus, which was classified as type B or type B and C. The center of the infiltrate consisted of a solid

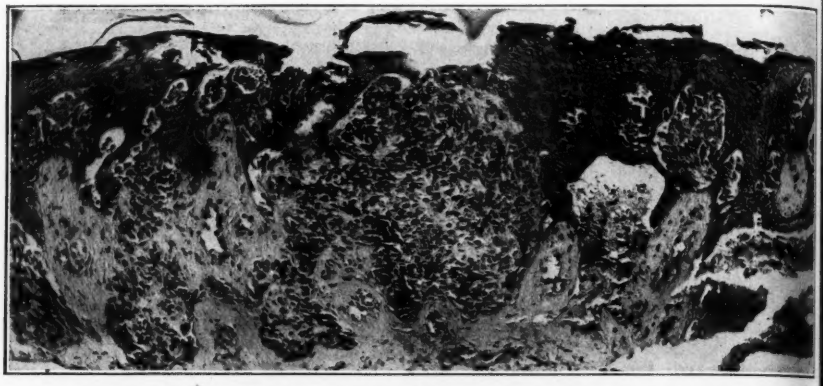


Fig. 6 (case 1).—Lentigo maligna. Melanoblasts have multiplied at the epidermodermal junction, have penetrated into the dermis and are being cast off through the epidermis. The last feature distinguishes the lesion from a nevus, although it has been called a junction nevus. Differentiation from a nevus is sometimes difficult. Low power lens; hemalum, erythrosin and saffron stain.

Fig. 7 (case 2).—Type B and C nevus at the periphery of the section. The cells in the center are multiplying and encroaching on the neighboring tissue, including the epidermis. A diagnosis of early melanoma was made, and the area was excised surgically. Low power lens; hemalum, erythrosin and saffron stain.

mass of cells which appeared somewhat encapsulated and seemed to be encroaching on the surrounding tissue, including the epidermis. Because of this apparent

tendency to proliferation, diagnosis was made of early melanoma, and the area was excised surgically. Four years after removal of the nevus, no sign of recurrence was present in the scar.

CASE 3.—L. C., a physician aged 32, stated that he had had a nevus on the lower left portion of the abdomen as long as he could remember. He stated that it was enlarging and that he had been advised to have it removed. On the lower left portion of the abdomen was a slightly elevated, yellowish lesion, 3.0 mm. in diameter, with a brown border 1.0 to 2.0 mm. wide. The lesion was removed by a cutaneous punch.

Microscopic section (fig. 8) showed that the epidermis was thinned, especially in the center of the section. Masses of nevus cells were present in the superficial portion of the dermis. Melanoblastic cells were more prominent than usual all along the epidermodermal junction, and in the center of the lesion such cells were arranged in masses evidently resulting from their multiplication. There was little evidence that such masses of cells were being cast off at the epidermal surface, as they are in lentigo maligna, but in one area a group of cells, presumably of this kind, was seen within the stratum corneum. Diagnosis was made of

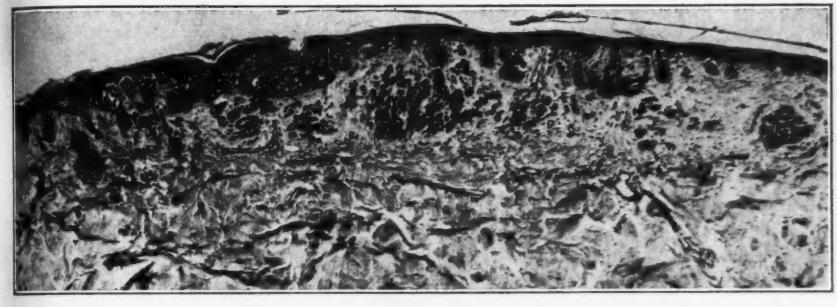


Fig. 8 (case 3).—Type A and B nevus. In one section a mass of nevus cells was seen in the stratum corneum, which finding suggested a diagnosis of lentigo maligna. Low power lens; hemalum, erythrosin and saffron stain.

nevus pigmentosus of the A and B types, with increased melanoblastic activity at the epidermodermal junction. This process of melanoblastic proliferation was considered still in the early stages and could not be definitely identified as malignant. However, prophylactic excision of the area was recommended and was carried out by an Army surgeon. The report created some excitement because of an Army regulation that dissection of the lymph node should accompany an operation for melanoma. The opinion of several Army pathologists vetoed such a procedure, and local excision of the area was considered sufficient. After two years, there has been no sign of local recurrence or metastasis.

CASE 4.[20]—A male student, aged 40, presented an elevated, dark brown lesion over the left zygoma, which growth, he stated, had been present as long as he could remember. It had recently increased in size. He presented a semiglobular tumor about 1.0 cm. in diameter. Because of the history of recent growth, it was excised.

20. Becker, S. W.: Melanotic Neoplasms of the Skin, Am. J. Cancer **22**:17, 1934.

Microscopic examination revealed a nevus of type A and B, at the periphery of which the groups and strands of nevus cells were of the usual variety. Toward the center, however, there were increasing numbers of fusiform, melanin-containing cells. In the center of the lesion the melanotic cells extended uninterruptedly from the epithelium to as deep as the nevus cells, or deeper. In addition, there was a large area of inflammatory infiltrate in one portion of the tumor. In silver preparations, the melanin-containing fusiform cells were more plainly seen.

The diagnosis was nevus pigmentosus with early melanoma. It is obvious that if such a lesion had been treated in a conservative manner, without biopsy and without destruction of all the deeper pigment-containing cells, further extension would probably have occurred. This may be the type of lesion in which treatment has been said to encourage the development of malignancy. However, biopsy showed that malignancy had already supervened.

CASE 5.[21]—A woman aged 30 had had a pigmented mole on the shin since birth. She gave the history that it had been enlarging for four months. It was excised.

Microscopic study showed that the lesion was a type B nevus with additional melanoblastic activity at the epidermodermal junction. At the periphery of the lesion, beyond the clinically hyperpigmented border, dendritic melanoblasts were seen, with melanosis of the basal palisade cells. This pigment activity was abnormal because the area had been exposed to no external agent, such as ultraviolet irradiation.

Toward the center of the lesion, dendritic cells were increased in number and appeared as though in vacuole-like spaces. The epidermis was more deeply pigmented. The melanoblasts extended in masses into the superficial dermis.

At the center of the lesion, the epidermis was disintegrated and decidedly hyperpigmented, even to the surface. Melanoblasts were further increased in number.

The diagnosis made was early melanoma, arising in a pigmented nevus.

COMMENT

Many of the statements made in this contribution depend on my own interpretation of the pigmentary processes. An obstacle that cannot be overcome rests in the fact that after the lesion has been destroyed any interpretation of what its further course might have been is based on surmise, since it is not feasible to remove part of a potentially malignant lesion and leave the rest of it in situ.

However, study of sections of lesions ranging all the way from benign moles to those of unquestionably malignant melanoma cultivates a degree of familiarity with the danger signs that must be watched. Unfortunately, not all general pathologists have had an opportunity to study sections representing such a wide range of disorders; hence some of the early danger signs may be missed by them.

The clinical picture alone cannot be depended on for evaluation; hence biopsy should be resorted to.

---

21. Becker, S. W.: Cutaneous Melanoma, Arch. Dermat. & Syph. **21**:818 (May) 1930.

Further study will be necessary to determine the pathologic nature of type C nevi and whether they should be called neurofibroma or schwannoma (Masson).

SUMMARY AND CONCLUSIONS

Treatment of pigmented nevi as recommended by dermatologists is contrasted with that suggested by surgeons and oncologists.

The microscopic changes in 741 specimens of nevi removed from 681 patients are presented, with a classification slightly modified from that of Miescher and von Albertini.

The clinical diagnosis agreed with the microscopic diagnosis in from 80 to 87 per cent of cases.

Nevi in which nevus cells are attached to the epidermis are more important from the standpoint of malignant change than are purely dermal nevi.

Type C nevi should be studied further.

Methods which combine treatment with biopsy are recommended, with subsequent surgical removal of the area if suspicious microscopic changes are noted.

Such methods should lessen to an irreducible minimum the incidence of melanoma formation following treatment of nevi.

Case reports which demonstrate some of the pitfalls in diagnosis and treatment are presented.

55 East Washington Street (2).

ABSTRACT OF DISCUSSION

DR. HARRY R. FOERSTER, Milwaukee: Dr. Becker's histologic classification as presented today, if generally adopted as a guide for therapeutic decision, should do much to clarify the controversial issue of what to do with the pigmented nevus.

As he states, it is essentially a matter of correct diagnosis and proper classification. I believe also that by careful histologic study of different clinical types of pigmented nevi the dermatologist should be able to develop a diagnostic acumen resulting in a high percentage of accurate clinical diagnoses, obviating the necessity of routine biopsies and permitting a clinical classification that might be correlative with the histologic one which has just been presented.

As a background for this discussion, I reviewed my office records of 57 cases of malignant melanoma and of 689 cases of pigmented nevi and have endeavored to place the latter in clinical groups analogous to Dr. Becker's outline. There is a striking parallelism in the percentages of these two series of histologic and clinical classifications.

Twelve and one-half per cent of the lesions in my series could be placed in the A or the A and B category and had been recorded as melanotic nevi, by which designation potential malignancy was implied. It has been the practice of my associates and myself to advocate surgical removal of these lesions, preferably by a plastic surgeon experienced in this field. It is this group, which includes the junction nevus described by Traub and the lentigo maligna, which has given the pigmented nevus its bad name and discredited dermatologic procedures.

In 44 per cent of our cases the lesion was recorded as nevus pigmentosus and would probably belong in the B or in the B and C group; 30 per cent were the pigmented and fibrous nevi of the B and C or the C category, and the remainder were miscellaneous forms.

The majority of the lesions of the B and the B and C type had been treated by electrodesiccation, some by solid carbon dioxide and some by surgical removal. Some had been subjected to biopsy and cautery, but when histologic study was desired surgical excision was usually advocated. I see no particular advantage to the patient in biopsy followed by cautery, as advocated by Dr. Becker, as a routine procedure in the treatment of the B and B and C types, and I believe that by referral of some of such cases to the surgeon for excision of the lesion a better understanding with surgeons will be arrived at regarding the benign character of this lesion and its suitability for dermatologic treatment.

The C group and the miscellaneous types had been variously treated by electrodesiccation, removal with cautery or surgical excision. In some instances nonintervention was advised. In only 1 case of our entire series have we knowledge of malignant growth following dermatologic treatment. In that instance a verrucous and pigmented nevus became a malignant melanoma eight years after original electrodesiccation and terminated fatally, in spite of surgical removal before demonstrable metastasis.

I believe that when malignancy develops in a pigmented nevus the cause is an inherent change in the physiology of cell metabolism and the mechanism of pigment formation. I believe that the role of single, and possibly of repeated, local injury and other irritation in the development of malignancy, except in facilitating dissemination of a metastasizing process, has in general been overstressed.

I agree with Dr. Becker also that the danger of dissemination by biopsy has been exaggerated, and I have not seen an instance of metastasis following such procedure in cases of malignant melanoma or in growing nevi of melanotic type.

Sealing the biopsy wound by electrodesiccation should be a helpful safeguard. I have likewise not observed any malignant growth develop directly after infection in a pigmented nevus or at the site of a nevus.

The records of cases of malignant melanoma present mute evidence of the futility of all forms of treatment in most such cases once they are advanced and teach one to respect the potential menace in certain nevi. But this fact should not deter one from treating dermatologically lesions that are definitely benign. It is startling to note the frequency with which an apparently slowly progressing melanotic malignant growth may become a fulminating process after radical surgical excision.

The inference is not that surgical intervention is responsible but that, as with some cases of so-called meddlesome nonsurgical treatment, it was merely an ill chosen procedure.

My colleagues and I have records of histologically proved cases of malignant melanoma in which the patients survived five years or more after radical excision and also after aggressive radium and roentgen treatment, when surgical intervention could not be satisfactorily applied. In some nevi that showed growth and increased pigmentation and that were unsuitable for surgical treatment, we were successful in reducing and inactivating lesions for many years, or permanently, by radium treatment.

In all cases, however, it should not be assumed too early that the treatment has been successful. I have seen malignant melanomas develop, recur or become reactivated from five to eight years after apparent destruction.

The dermatologist must tread lightly in the field of the melanomas, but he can find encouragement for his restricted procedures with pigmented nevi if he will follow the methods of classification and therapeutic procedures outlined by Dr. Becker in his excellent and important contribution.

DR. NORMAN N. EPSTEIN, San Francisco: The treatment of melanoma is worthy of our deepest consideration. Personally, I do not think that the best job possible is being done with these lesions. There are, of course, certain factors that contribute to one's inability to determine clinically whether a nevus is malignant or not.

I feel, like Dr. Foerster, that the malignancy in a nevus is inherent and probably exists from the early development of the lesion. It is probable that what is done to the lesion does not contribute greatly to the development of a malignant process. These lesions may be malignant in an arrested form for many years and, because of factors that are not understood, begin to show malignant activity and growth.

One of the most important factors in the education of the dermatologist, the surgeon and the roentgenologist is the visible tumor clinics, where all may look at the same lesion and determine the proper treatment. A few years of such experience makes for greater efficiency in the diagnosis and management of the lesion. Surgeons become conscious of their responsibility with this type of lesion when they sit in, week after week, on consultations and discussions with the dermatologist and the roentgenologist.

If there is any suggestion that the lesion might be malignant, I agree with Dr. Foerster that it is well to take a small piece for biopsy. If the growth is malignant, no great harm is done.

The question of biopsy was brought up in regard to melanoma. It is important that we extend our ideas in that regard to other lesions of possible malignant potentiality. I believe that a biopsy should be made of every lesion that might be melanoma or carcinoma, even though the lesion might appear benign clinically.

It is discouraging when, months or years later, a patient with a previously treated melanoma comes into the visible tumor clinic with evidence of recurrence and it is found that no pathologic examination was made originally. The further treatment in the case may be difficult to decide on.

I think surgical intervention is the proper approach to treatment of melanoma, and it is surprising how long the life of the patient may be prolonged even when obvious metastases are present.

DR. LOUIS H. WINER, Beverly Hills, Calif.: Removal of a specimen for biopsy has never caused a lesion to become malignant.

The upward proliferation of the cells is interesting, but the downward penetration and the tendency to broaden out toward the lower borders, as well as the increase in the number of mitotic figures, are to me just as indicative of a malignant melanoma.

With regard to group 3, I am sorry Dr. Becker did not have more work done on that type, for it brings to mind a case presented at the Los Angeles Dermatological Society of a lesion in which there were two proliferative elements, epidermal and collagenous—in other words, a malignant melanocarcinoma or sarcoma.

It is perhaps necessary to educate the public against letting these lesions be treated by the inexperienced.

I think that to make biopsies of all elevated lesions is a little extreme and impractical. It would, of course, be desirable to have the information the

biopsy would furnish, but one must remember that some persons have large numbers of these nevi which are elevated and acquired.

Moreover, the biopsy reports are not always reliable; there is a difference of opinion among persons here as to the interpretation of the features and the signs of malignancy. Dr. Becker emphasizes the growth upward through the epidermis; others think that the growth downward is equally important.

It would be good if all pathologists and dermatologists agreed on what constitutes malignancy in these cases. In one of my patients a black growth developed in a path of radiodermatitis on his ear. Biopsy diagnosis of malignant melanoma was made by two good pathologists. The man, however, would not submit to operation and insisted that a 5 per cent yellow mercuric oxide ointment U.S.P. had cured everything he had ever had. The lesion disappeared, and he has had no further trouble from it.

Dr. George C. Andrews, New York: I enjoyed Dr. Becker's paper and wish to compliment him on an excellent piece of work. It will simplify the classification and increase understanding of these nevi.

I am not particularly worried about the patients who go to Dr. Becker and the dermatologists in this room. Such patients on the whole, and almost 100 per cent, have a good diagnosis and are treated successfully.

However, that statement does not apply to other dermatologists who are not so experienced, or to the dentists, barbers and beauty parlor operators who treat these nevi, or to surgeons who have had little experience and still treat these nevi. Whereas some surgeons have had relatively little experience in this field, others have taken special interest in it.

Dr. C. Guy Lane, Boston: I wish to endorse Dr. Epstein's comment with regard to the diagnosis of these and other tumors of the skin in a tumor clinic. Massachusetts General Hospital has had a tumor clinic for twenty years, and there the plastic surgeons, the roentgenologists and the dermatologists confer on practically all cases. I also endorse Dr. Foerster's remarks with regard to the matter of excision versus biopsy. It is perhaps not necessary to refer all these cases to the plastic surgeon, although it has been my practice for some time to do so when I think an operation by a plastic surgeon will give the best results. I should like to make a plea for the training of young dermatologists in at least the principles of plastic surgery, as is being done at the New York Post Graduate Medical School and Hospital. I believe that many of these young men can learn to handle the simpler cases adequately.

Dr. S. William Becker, Chicago: It may be true that routine biopsy is not necessary, but only in this way have I learned about these tumors. As Dr. Pusey often said, one must overemphasize for effect. If one recommends that biopsy be done on all nevi, the ordinary physician might perform biopsy on a few of them.

In cases in which the diagnosis of melanoma has been made, I have made an effort to get a section of the so-called mole which had been removed; when such specimens have been obtained, they have often been shown to be malignant. It has been alleged that inflammation predisposes to malignant changes, but in 16 of my cases inflammation was present and there was no sign of malignancy.

Dr. Foerster states that malignant change is slow. It is the general opinion that the spread of the melanoma or the malignant change is rapid; that I think is fallacious. These premelanotic stages may be present for many years. Several years ago I reported the case of a young girl who had had a lesion on her foot for eight years. There was no metastasis, but after operation a malignant change did develop.

Dr. Epstein stated that he was not sure why some people have malignant lesions, but certain things have been demonstrated. Malignant melanoma is practically unknown before puberty, and in many instances the influence of menstruation and pregnancy has evidently been an important factor. I agree with Dr. Epstein that biopsy is important. I have never treated a tumor of the skin without biopsy.

The tumor clinics have an important place, for interchange of ideas is what is most needed.

I agree with Dr. Winer as to the harmlessness of biopsy tissue. I do not believe that the removal of tissue for biopsy is at all dangerous, because the inflammatory reaction following it actually seals off and prevents dissemination of the lesion, rather than opens it.

As Dr. Andrews said, the education of all concerned, including the public, is important.

PORPHYRIA WITH CUTANEOUS MANIFESTATIONS

LOUIS A. BRUNSTING, M.D.
AND
HAROLD L. MASON, Ph.D
ROCHESTER, MINN.

PORPHYRIA is that rare familial metabolic fault in which abnormal kinds and amounts of porphyrins, especially uroporphyrin, are excreted in the urine and feces. The disease may be latent or asymptomatic for years or for life, and the urine may or may not have an abnormal coloration. Surveys of families in which porphyria occurs may disclose the presence of uroporphyrin or the colorless porphobilinogen in the urine of apparently normal persons. Although the chemistry and physiology of the porphyrins are complex, the performance of tests, at least of the qualitative tests for urinary porphyrins, is not beyond the range of most laboratory facilities.

Porphyria finds clinical expression in various forms: the acute type, in which intermittent episodes of serious gastrointestinal or nervous and mental symptoms occur; the rare congenital type, which may begin in earliest childhood with symptoms such as redness of urine, erythrodontia, a hydroa-like, mutilating eruption of the skin which is exposed to light and sometimes visceral complications, and the intermediate or chronic types, in which symptoms referable to the gastrointestinal tract, the nervous system or the skin are milder. Symptoms of intermediate or chronic porphyria may be similar to those of either the acute or the congenital type and usually occur in adults. Chronic porphyria may represent a tardive form of the congenital type.

Little is known concerning the factors which may precipitate the syndrome of porphyria or influence its course in one way or the other. In certain cases a damaging influence on the liver, either by disease, such as cirrhosis, or by hepatotoxic drugs or poisons (alcohol), appears to contribute to the development of the manifest phase of porphyria.

In acute porphyria, the skin is seldom involved; in congenital porphyria in children, the exposed skin is mutilated by a photosensitive

From the Section on Dermatology and Syphilology (Dr. Brunsting) and the Division of Biochemistry (Dr. Mason), the Mayo Clinic.

Read before the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 4, 1947.

reaction. In chronic porphyria, the disease may first become manifest in adult life, in the form of a bullous reaction of the skin which simulates that in epidermolysis bullosa, in which the exposed surfaces are sensitive to light and to trauma. Pigmentation and hypertrichosis may occur. Also, intermittent episodes of abdominal colic may occur, and nervous or mental disorders may develop.

Recently we reported [1] a case of chronic porphyria in which the patient was a woman aged 58 who had a long record of a vague psychic disorder coupled with chronic alcoholism. In the eighteen months prior to her admission a mild blistering reaction of the skin which was exposed to light occasionally had occurred and the patient had lost considerable weight. Large amounts of uroporphyrin were discovered in the urine. A subsequent report from the patient indicated that since our report, in the ensuing two or three years, she had shown pronounced improvement on treatment consisting of an anticirrhotic regimen and the abstinence from use of alcohol. The patient's sister was found to have latent porphyria.

The pernicious influence of alcohol in precipitating the clinical phase of chronic porphyria is emphasized by the report of Szodoray and Sümegi,[2] who observed 12 cases in which it was a factor in Hungary during the war years. Ten men and 2 women, between 26 and 64 years of age, all of whom had chronic alcoholism, presented the characteristic blistering of the skin and porphyrinuria. Syphilis was present in half the cases.

Of a series of 12 cases of porphyria recorded by Barnes [3] from South Africa, a bullous reaction of the skin and pigmentation were prominent symptoms in 6. Two of the patients were sisters.

In a short monograph, Borda [4] discussed the cutaneous signs of porphyria and described "a blistering or pigmented erosive porphyria of the adult" in 3 men and 3 women in Argentina. In 1 instance melanosis was the presenting symptom; in 2 others melanosis and hypertrichosis accompanied the blistering eruption. No familial inci-

1. Brunsting, L. A., and Mason, H. L.: Porphyria with Epidermolysis Bullosa: Report of a Case of the Tardive Congenital Type with Demonstration of Latent Porphyria in a Sister of the Patient, J. A. M. A. **132**:509-513 (Nov. 2) 1946.

2. Szodoray, L., and Sümegi, S.: Ueber die Nosologie der chronischen kutanen Porphyrie, Dermatologica **90**:224-232, 1944.

3. Barnes, H. D.: A Note on Porphyrinuria with a Résumé of Eleven South African Cases, Clin. Proc. **4**:269-275 (July) 1945.

4. Borda, J. M. C.: Porfirinas y porfiria: Consideraciones especiales sobre clinica y clasificacion de dermatosis porfiricas, Buenos Aires, Lopez & Etchegoyen S.R.L., 1946.

dence was noted, nor was alcoholism mentioned; in several cases the urine was described as having the color of red wine.

Occasionally, intermittent episodes of obscure abdominal colic, such as occur in acute porphyria, may precede or overshadow the cutaneous signs of chronic porphyria, as in the case reported by Taylor and his colleagues.[5] Their patient passed through a normal pregnancy without incident to mother or child.[6] Not infrequently, the abdominal crises of porphyria lead the unwary surgeon to the performance of useless exploratory laparotomy, Kuske's [7] patient, who underwent many operations, being a case in point. In that case, the patient gave a long history of abdominal cramps, as well as of psychic and nervous disorders, and later she had "chronic bullosis actinica et mechanica" and two episodes of acute photodermatitis due to exposure to sunlight.

It may be practically impossible to distinguish acute from chronic porphyria on the basis of clinical symptoms or of the laboratory analysis of the excreted porphyrins. Waldenström [8] emphasized that in his extensive experience with acute porphyria in Sweden he had not encountered any instances of congenital porphyria, and, while pigmentation frequently had occurred in the cases he had seen, no instance of photosensitivity had been observed. He contended further [9] that the presence of the colorless chromogen porphobilinogen is a distinctive feature of cases of acute porphyria, either in the manifest or in the latent phase of the disease. In view of the work of Watson and his collaborators,[10] it is doubtful whether the type of clinical manifestation is dependent on the type of isomer of porphyrin excreted in the urine or feces.

---

5. Taylor, I. J.; Solomon, M. L.; Weiland, G. S., and Figge, F. H. J.: Chronic Porphyria, J. A. M. A. **131**:26-29 (May 4) 1946.

6. Linas, S.; Solomon, M. L., and Figge, F. H. J.: Chronic Porphyria Complicated by Pregnancy, J. A. M. A. **133**:105-107 (Jan. 11) 1947.

7. Kuske, H.: Zum Problem der Hautveränderungen bei Porphyrie, Dermatologica **92**:149-157 (June-July) 1946.

8. Waldenström, J.: Studien über Porphyrie, Acta med. Scandinav., 1937, supp. 82, pp. 1-254.

9. Waldenström, J., and Vahlquist, B.: Studies on the Excretion of Porphobilinogen in Patients with So-Called Acute Porphyria, Acta med. Scandinav. **117**:1-14, 1944.

10. Grinstein, M.; Schwartz, S., and Watson, C. J.: Studies of the Uroporphyrims: I. The Purification of Uroporphyrin I and the Nature of Waldenström's Uroporphyrin, as Isolated from Porphyrin Material, J. Biol. Chem. **157**:323-344 (Jan.) 1945. Watson, C. J.; Schwartz, S., and Hawkinson, V.: Studies of the Uroporphyrism: II. Further Studies of the Porphyrins of the Urine, Feces, Bile and Liver in Cases of Porphyria, with Particular Reference to a Waldenström Type Prophyrin Behaving as an Entity on the Tswett Column, ibid. **157**:345-361 (Jan.) 1945.

The distinctions may not be clearcut; exceptions do occur. The case of fatal acute porphyria reported by Nesbitt and Watkins [11] presented bullous and urticarial reactions to light. One of Barnes's patients, who died of ascending paralysis from porphyria, had had a blistering reaction of the hands for several months. The case reported by Kuske suggests acute porphyria with photosensitization, although the laboratory data are incomplete.

In this paper, we wish to report 3 additional cases of porphyria with cutaneous manifestations. In each instance a history of chronic alcoholism and evidence of hepatic dysfunction which it seemed reasonable to blame for the precipitation of the clinical symptoms were present. Two of the patients had a mild cutaneous reaction on the exposed skin and uroporphyrin in the urine; their cases are examples of chronic porphyria. The other patient had, in addition to the aforementioned symptoms, a severe episode of abdominal colic and porphobilinogen in the urine; his case is an example of acute porphyria. Also, in the last-mentioned case we were able to demonstrate that the mother of the patient had latent porphyria.

METHODS OF DETERMINATION OF PORPHYRINS IN URINE

Before giving the details of the 3 cases, we should like to describe the methods of examination of the urine for porphyrins.

Qualitative Examination.—In a case in which it is suspected that porphyria is present, the urine is acidified with hydrochloric acid and examined visually for fluorescence in the light beam of the Pfaltz and Bauer fluorophotometer. The incident beam is passed through Corning filter 5113 (old number 511). If a fluorescence is visible, another portion of the urine is acidified with acetic acid and extracted with ether. If there is a residual red fluorescence in the aqueous layer which is not removed by further extraction with ether, it is considered to be evidence of the presence of uroporphyrin.

Another portion of urine is tested for porphobilinogen by the method of Watson and Schwartz.[12]

Quantitative Determinations.—The method of Mason and Nesbitt [13] was used for the determination of coproporphyrin.

Only a rough estimate of the amount of uroporphyrin is obtained. Hydrochloric acid is added to the residue of urine after extraction with ether for the determination of the amount of coproporphyrin, the quantity added being sufficient to make the concentration of hydrochloric acid 5 per cent. The resulting solution is then diluted with a 5 per cent solution of hydrochloric acid until

11. Nesbitt, S., and Watkins, C. H.: Acute Porphyria, Am. J. M. Soc. **203**:74-83 (Jan.) 1942. Berg, M.: Acute Porphyria; Clinical and Pathologic Observations, Arch. Int. Med. **76**:335-340 (Nov.-Dec.) 1945.

12. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. **47**:393-394 (June) 1941.

13. Mason, H. L., and Nesbitt, S.: A Method for the Determination of Coproporphyrin in Urine, J. Biol. Chem. **152**:19-25 (Jan.) 1944.

the concentration of porphyrin is less than 0.03 microgram per cubic centimeter as judged by the fluorescence as compared with the coproporphyrin standard. The fluorescence is measured; the solution is diluted once or twice more, and the fluorescence is measured again. If the dilution is sufficiently great, the effect of substances that quench or otherwise interfere with the fluorescence is diluted out, and the fluorescence is inversely proportional to the dilution. If the initial concentration of uroporphyrin is small, it is impossible to dilute out the effects of other urinary constituents. The results so obtained are probably minimal, since the effect of other urinary constituents is to depress the fluorescence of the porphyrin.

The color produced by the method of Watson and Schwartz, after the extraction of the reaction mixture with chloroform to remove the color due to the urobilinogen aldehyde, is measured in a Klett-Summerson colorimeter with a filter transmitting maximally at a wavelength of 565 millimicrons. The control is prepared by addition of the reagents in reverse order to the urine, followed by extraction with chloroform. Since the color produced is similar to that due to the urobilinogen aldehyde, the results are expressed as porphobilinogen units, a unit being the color equivalent of 1 mg. of urobilinogen.

REPORT OF CASES

CASE 1.[14]—A farmer aged 20 was admitted to the Mayo Clinic on Aug. 15, 1946. He complained of a mild blistering eruption on the back of his hands and fingers, which lesion had appeared intermittently during the preceding summer months. On one or two occasions a few blisters had appeared on the back of his neck. After he had worked in the sun for a day, his hands would itch, and the next morning a few scattered vesicles would be present. He had also noted that blisters appeared after casual trauma in these sites.

The patient's general health was otherwise excellent. The patient related that he had drunk alcohol in fairly large quantities on two or three occasions each week for the preceding two or three years. The family history was without incident except that the maternal grandfather, an alcoholic addict, had died of a disease manifested by obscure abdominal symptoms. Both parents, two brothers and two sisters were alive and well.

On examination, the patient seemed in good physical condition, the exposed skin presenting a healthy farmer's tan. On the dorsa of the fingers and hands were a few infected excoriations, a ruptured hemorrhagic bulla and one or two small, clear vesicles. Nikolsky's sign was not present. The palms were normal. On the face, the skin of the nose, the nasolabial folds, the chin, the lower part of the cheeks and the central part of the forehead, the skin was slightly roughened and thickened as the result of a low grade, diffuse, verrucose process, and had a translucent quality and was yellowish. Biopsy of the skin of the left side of the tip of the nose revealed microscopic changes in the connective tissue suggestive of a colloid milium.

The patient was instructed to protect his skin from direct sunlight but neglected these precautions, and from time to time, after exposure, new blisters developed on his hands, a few on his neck, and one on his elbows after he had been in the sunlight with his sleeves rolled up. Attempts to reproduce such lesions with artificial light (by carbon arc lamp) failed. There had been no unusual discoloration of the urine. A sample, examined Sept. 13, 1946, was

14. Presented at the meeting of the Minnesota Dermatologic Society, Rochester, Minn., Sept. 15, 1946.

found to be free from porphyrins, although a faint trace of color was noted when the test for porphobilinogen was carried out.

On Nov. 1, 1946, the patient again registered at the clinic and was hospitalized. For a few days he had had abdominal symptoms suggestive of those of acute appendicitis. He thought, too, that he had passed blood in his urine. The abdominal pain persisted as a deep-seated, burning distress in the epigastric region and in both lower abdominal quadrants but was not particularly localized. Anorexia and slight nausea were noted, but the patient did not vomit. The abdomen was soft. The temperature and pulse rate were normal, and slight leukocytosis was observed, but the sedimentation rate of the erythrocytes was not elevated. The first specimen of urine was cherry red; routine urinalysis gave results within the normal ranges, but special study for porphyrins revealed a strongly positive primary fluorescence, and the result of the test for porphobilinogen was positive.

Fig. 1 (case 1).—(*a*) On Nov. 2, 1946, the face showed only a few crusted, infected lesions. (*b*) On November 8, the face was edematous and at the height of the vesicular reaction.

When the patient was admitted to the hospital a few crusted lesions on the face (fig. 1*a*) and hands and several larger denuded areas on the right forearm and one on the back of the neck, at the sites of receding furuncles, were observed. Small milia were present on the forehead, nose and knuckles. Biopsies of skin from the dorsum of the right index finger and from the left hand were made on November 5. Melanin pigmentation in the basal layers of the epidermis was increased. In the upper cutis the connective tissue assumed a bluish tint, and the fibers of collagen merged with the elastic tissue. The results of chemical examination of the skin for porphyrin were negative.

For the first few days that the patient was in the hospital, the abdominal pain was intermittent and only moderately severe; on the third day it assumed the nature of cramps and colic and became localized to the lower abdominal quadrants, with extension to the testes. With this development, vomiting began; at first the patient vomited two or three times in twenty-four hours and then, gradually, oftener.

On the sixth day he became critically ill, and a combination of unusual symptoms arose, lasting a week and then gradually tapering off. The patient began to have a fever daily, the temperature reaching 103 to 104 F.; the blood pressure maintained a level above normal, ranging from 160 to 198 mm. of mercury systolic and from 90 to 120 mm. diastolic. Abdominal colic with nausea and vomiting was almost continual, and it was necessary for the patient to be given large doses of narcotics and to be fed intravenously. Obstipation was severe; one stool was passed on the seventh and one on the fifteenth day.

Only the first specimen of urine was red. Subsequent specimens were amber colored and darkened on standing, but later the urine was normal in color.

Made shortly after the admission of the patient, the sulfobromophthalein test for hepatic function revealed a 24 per cent retention of the dye; on November 14,

Fig. 2 (case 1).—On Nov. 2, 1946, the hands showed old and recent lesions of porphyria, with scars, milia and new and old bullae, some of them ruptured, hemorrhagic and infected.

at the peak of the acute reaction, there was total retention of the dye, but still no evidence of jaundice was discernible. The direct and indirect van den Bergh tests gave only a slightly positive reaction. Other laboratory values were within normal limits.

Beginning with the fever on the sixth day the most striking changes in the skin also became apparent. These were in the form of an acute episode of edema and vesiculation of the face and neck. There had been no sunlight for three days previously; the patient was in a room with northern exposure, and if any daylight reached him it was filtered through window glass which was at least 4 feet (1.2 meters) from his head. The skin of the face began to swell in circumscribed dollar-sized (3.8 cm.) patches, resembling those in angioneurotic edema, beginning on the sides of the nose, the cheeks and the midforehead. Within a few hours a cluster of herpetic vesicles appeared in the

swellings, and the process progressed day by day. The patches coalesced until by the end of a week the face, except the upper part of the forehead, was edematous and vesiculated and the condition resembled dermatitis venenata in the acute phase (fig. 1*b*). The process extended to the sides of the neck but did not involve the hands or the trunk. On the hands the crusted lesions assumed an ecthymatous character (fig. 2), but no new lesions appeared. During this acute stage the Nikolsky sign could be elicited on the skin of the hands.

The honey-colored exudate from the lesions on the face and hands when examined by Wood light in a darkened room revealed a bright red fluorescence. The same color was noted in the secretions of the mouth, between the teeth and on the dorsum of the tongue. Examination of specimens of the feces revealed orange-red fluorescence.

Examination of the blood on November 6 revealed 11.5 micrograms of porphyrins in the erythrocytes and 22.3 micrograms in the plasma, per hundred cubic centimeters of blood. The two specimens of stool, of November 7 and 15, contained

Porphyrins in Twenty-Four Hour Samples of Urine in Case 1

Rate	Coproporphyrin, Mg./24 Hr.	Uroporphyrin, Mg./24 Hr.	Porphobilinogen, Units/24 Hr.
1946			
September 13	...	...	Trace
November 3	7.0	5.7	14.0
November 5	5.5	2.9	8.1
November 10	13.4	9.4	22.8
November 12	11.7	6.3	6.5
November 14	....	...	4.7
November 15	....	...	6.4
November 18	4.5	1.4	0
November 21	5.9	1.7	3.7
November 24	5.1	1.3	0
1947			
February 22	5.4	1.4	6.4
April 25	3.8	0	0

44.9 and 61.7 mg., respectively, of coproporphyrin. There was also evidence of an acetic acid-ether insoluble porphyrin in the stools, but the amount was too small to be measured. A summary of the values for porphyrins in the urine in this case is given in the accompanying table.

Toward the end of the second week that the patient was in the hospital, the symptoms of acute illness subsided. The temperature returned to normal on the eleventh day; the last attack of abdominal pain was on the fourteenth day. Intravenous feeding was discontinued, but the patient was given dietary supplements, a restriction of fats in the diet and a series of intramuscular injections of bejectal® [15] and liver extract. On the twenty-seventh day he was dismissed from the hospital. He had lost 30 pounds (13.6 Kg.). The area of acute dermatitis of the face was in the process of exfoliation, and the edema had subsided.

During the ensuing six months the patient made a steady gain in health and in well-being, and his weight returned to normal. For three or four months

15. One cubic centimeter of the injectable solution contains 10 mg. of thiamine hydrochloride, 75 mg. of nicotinamide, 2 mg. of riboflavin, 5 mg. of pyridoxine hydrochloride and 5 mg. of calcium pantothenate.

the skin in the exposed areas showed a slight tendency to vesiculation and to rubbing off after minor injuries, but this condition gradually subsided. Just prior to this report the patient was observed at the clinic; he stated that he had resumed his farm labors and had been exposed to the sun without undue reaction except for the appearance of a few vesicles on one hand on one occasion. A few scattered milia remained on his face and hands, but the signs of colloid degeneration of the skin of the face had largely disappeared. The laboratory evidence of hepatic dysfunction persisted; the dye retention test, carried out on April 23, 1947, showed about 12 per cent retention of the dye. The reaction to the cephalin-cholesterol flocculation test was plus 4. Examination of the urine still revealed large amounts of coproporphyrin, but the tests for uroporphyrin and porphobilinogen gave negative results.

Examination of the Family.—Members of the patient's family, with the possible exception of one of his grandfathers, had not had symptoms of porphyria. As has been mentioned, the maternal grandfather of the patient, who had been moderately addicted to alcohol, had died in his fifties of a disease which had produced obscure abdominal symptoms. Neither photosensitive reactions nor discoloration of urine had been noted in his case. Twenty-four hour samples of urine were collected from twenty-five immediate relatives—the parents, the maternal grandmother, the mother's five siblings, the patient's four siblings and the thirteen living maternal cousins of the patient. Analysis for porphyrins gave negative results for all but the mother. The mother of the patient was 46 years old and was entirely well. She had had mild eczema in 1942. Her urine was examined on three occasions, Nov. 7, 1946 and Feb. 22 and April 25, 1947, and was found to contain the following substances on these respective dates: coproporphyrin, 0.4 mg., test not made, 0.99 mg.; uroporphyrin, trace, trace, none; porphobilinogen, trace, 1.4 units, none.

Summary.—A young farmer with mild cutaneous symptoms of chronic porphyria suddenly began to have episodes of abdominal colic, fever and characteristic urinary findings of acute porphyria, as well as a violent blistering eruption of the face, presumably a reaction of photosensitivity. The patient was mildly addicted to alcohol, and evidence of hepatic dysfunction without jaundice was found. The patient's mother was found to have latent porphyria.

CASE 2.—A man aged 54, a fruit grower from Arkansas, presented himself at the clinic on Nov. 20, 1946, because of an eruption on the skin of his hands, of about six months' duration. During the previous months he had become aware of a tendency toward blistering of the skin of his hands and wrists, particularly after exposure to strong sunlight. He noted, too, that the skin of these parts rubbed off readily; minor trauma would provoke a blister, which sooner or later became hemorrhagic. His general health was otherwise good. For a number of years he had been a heavy drinker at times. The family history was not contributory.

When the blisters had first appeared, the diagnosis of pemphigus had been considered, and the patient had been given three intravenous injections of an arsenical preparation. Later he had come under the care of Dr. Charles H. Lutterloh, who had recognized that the symptoms might be manifestations of chronic porphyria and had referred the patient to us.

Examination revealed that the exposed skin was hyperpigmented, more so on the hands than on the face. The dorsa of the hands were deeply pigmented from the wrists to the finger tips, and scattered areas of superficially healed, depigmented scars were present. Milia were present in a few of these scars over the knuckles. There were a few scattered crusted lesions at the sites of

ruptured bullae. A few small, clear vesicles on the fingers and one broken, dime-sized (1.8 cm.) bulla on the hand, which lesion showed remnants of hemorrhage, were observed.

Tests for photosensitivity on the volar surface of the forearms, with the use of a carbon arc lamp as the source of light, showed no unusual reaction.

The sulfobromophthalein test for hepatic function showed a dye retention of 24 per cent. Jaundice was not present, and reactions to the van den Bergh test were normal.

The urine was acid and of normal color. Two twenty-four hour specimens were examined for porphyrins. The first showed coproporphyrin, 1.3 mg.; uroporphyrin, 4.8 mg., and porphobilinogen, 3.8 units; the second showed coproporphyrin, 0.8 mg.; uroporphyrin, 3.4 mg., and porphobilinogen, none.

The patient was advised to protect his skin from the sun, to abstain from drinking alcohol and to follow a regimen as in the treatment of cirrhosis—that is, restriction of fats in the diet and the addition of vitamin supplements, especially those of the vitamin B complex.

Summary.—In this case a mild, blistering, light-sensitive reaction of the hands, occurring for the first time when the patient was 54 years of age, was the first sign of chronic porphyria in a seemingly healthy man. Urinary findings were typical of those in porphyria. Laboratory evidence of hepatic dysfunction was found; the patient was moderately addicted to alcohol.

CASE 3.—A man, aged 41, presented himself at the clinic on account of a blistering reaction of the skin of the uncovered surfaces of the hands, neck and face after exposure to sun or on sustaining minor trauma. Small blisters would arise, increase to the size of a dime (1.8 cm.) and then fill with blood unless they were ruptured. Also, the color of the skin of the affected regions had darkened. With the onset of puberty the patient, who had been red haired, had become a brunet within the course of four or five years. His general health had been good. He had been a heavy drinker at intervals for more than ten years.

The patient's mother had been operated on three times for obscure abdominal colic and had not been relieved. A brother was said to have the same sort of abdominal symptoms.

The patient was a brunet and seemed to be of swarthy complexion, but actually only the exposed skin was heavily pigmented. Small pits on the face and neck at the sites of excoriations were numerous, and several scattered and crusted lesions were present. A few milia were seen on the face and fingers. On the dorsa of the hands there were a few dime-sized, infected excoriations and ruptured bullae. Nikolsky's sign was elicited on the hands.

Exposure of the dorsum of the left hand and of the skin of the back to light from a carbon arc lamp brought about no unusual reaction.

The general physical examination revealed no abnormalities except a mild degree of hypertension. The results of usual laboratory tests were within the normal ranges. The sulfobromophthalein test for hepatic function showed a retention of 24 per cent. The thymol turbidity test and the cephalin-cholesterol test of hepatic function gave normal results.

The urine was acid and dark reddish brown. Two twenty-four hour specimens were analyzed for porphyrins. The first showed coproporphyrin, 2.5 mg., and uroporphyrin, 10.3 mg., and the second, coproporphyrin, 1.8 mg., and uroporphyrin, 9.0 mg., per hundred cubic centimeters. The test for porphobilinogen gave negative results in both specimens.

Biopsies were made of the covered skin of the right shoulder and of the exposed surface of the left side of the neck. The first specimen was entirely

normal; examination of the second showed that the epidermis was essentially normal except for hyperpigmentation. In the upper cutis the change in the connective tissue was similar to that seen in senile skin. The staining reaction was slightly basophilic; the collagen and elastic fibers were merged, and there was some fragmentation of the elastic tissue in the papillary layers.

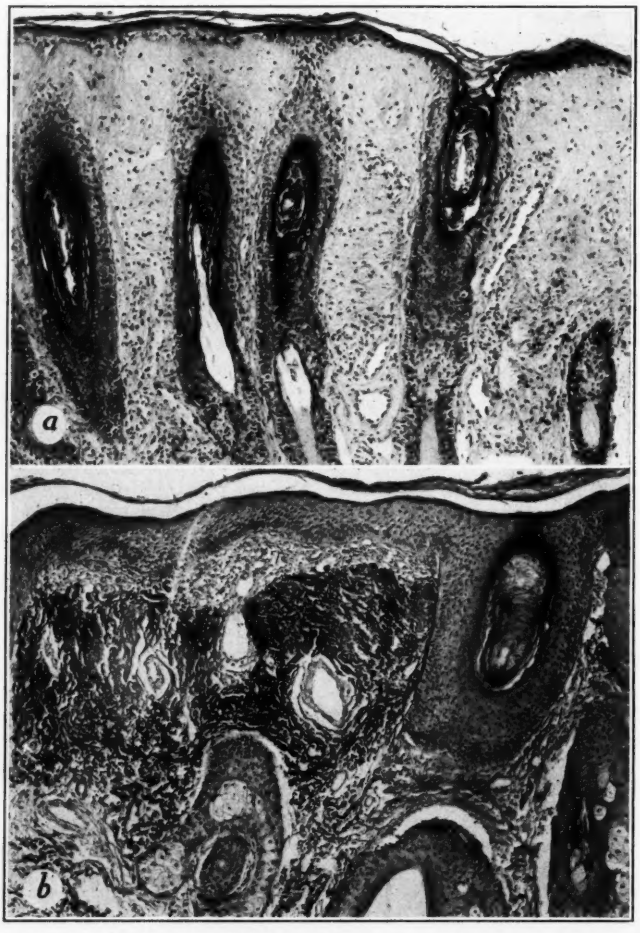


Fig. 3.—(*a*) Section from the skin of the nose. A homogeneous, colloid-like substance, staining pinkish with hematoxylin and eosin, is found in the papillary portion. Note the dilatation of the capillaries and the lymphatics (× 70). (*b*) Section from the skin of the shoulder. Elastin H stain shows the mingling of collagen and elastic tissue fibers with normal elastic tissue fibers at the bottom of the section, as well as dilated capillaries and lymphatics (× 65).

The patient was advised to protect himself from sun and to abstain from drinking alcohol and was given dietary advice similar to that given in cases of cirrhosis.

Summary.—A man, aged 41, presented symptoms of typical cutaneous pigmentation of four years' duration. A tendency for bullae to develop on skin exposed to light and/or trauma was noted. These lesions were considered the manifest signs of chronic porphyria. The changes in the urine were typical of those in cases of porphyria. Hepatic function was impaired, and a history of alcoholism was given.

MICROSCOPIC EXAMINATION OF THE SKIN

CASE 1.—Biopsy of the skin of the nose revealed few epidermal changes except for increased pigmentation and slight liquefaction degeneration of the basal layer. The rete ridges were somewhat flattened except in the vicinity of the hair follicles. The papillary and subpapillary layers of the cutis showed amorphous, irregularly shaped and poorly outlined masses, with a few nuclei scattered here and there (fig. 3*a*). The material stained light blue-pink with hematoxylin and eosin. In the center of the masses the elastin H stain showed that the elastic tissue was lacking; at their borders fragmented elastic tissue was collected in clumps with the collagen. The fibers of collagen were swollen and stained poorly. Lymph spaces in the upper cutis were dilated. There was no appreciable inflammatory reaction. The accessory structures of the skin were normal. Methyl violet and congo red stains revealed no amyloid. Biopsy of skin from the right index finger and from the left hand revealed no abnormalities except increased pigmentation in the epidermis. In the cutis, the collagen stained poorly and with a pinkish blue cast, and the fibers were homogenized. The collagen and the elastic fibers intermingled, but otherwise the elastic fibers were somewhat thin and not numerous. The appendages were normal.

CASE 3.—Biopsy of skin from the right shoulder revealed an essentially normal condition. Biopsy of skin from the left side of the neck revealed no abnormalities in the epidermis except hyperpigmentation, which was demonstrated best with the Becker stain. The cells of the basal layer were filled with dense granules of melanin, which overflowed somewhat into the squamous layer. In the upper portion of the cutis the hematoxylin-eosin stain gave a light blue color to the connective tissue; mucicarmine stain showed that mucin was not present. The collagen fibers were somewhat homogeneous and ill defined. Elastin H stain gave the elastic fibers in the upper portion of the cutis a reddish blue color; they were thick and swollen and mingled with the collagen (fig. 3*b*). In the deeper part of the cutis the elastic fibers were normal. Methyl violet and congo red stains did not reveal amyloid.

COMMENT

The changes which occur in the skin in chronic porphyria are melanosis, hypertrichosis, milia and a chemical and physical alteration of the connective tissue, which renders the surface layers susceptible to trauma and gives rise to a blistering reaction to light. Only the exposed skin is so affected, presumably through the toxic influence of cumulative doses of light, although the blisters cannot well be reproduced by artificial means and cannot be reproduced at all on the skin that has been protected from light. These changes occur also in epidermolysis bullosa, which is likewise an inherited abnormality of the skin, but the two conditions are entirely distinct. In cases of

epidermolysis bullosa, trauma alone is the precipitating agent, and the pressure surfaces, such as the palms and soles, are primarily involved. It would be better to describe the cutaneous manifestations of porphyria as "bullosis actinica et mechanica."

In porphyria, even on the surfaces exposed to light, blistering is a late manifestation, and the Nikolsky phenomenon can be elicited irregularly, if at all. To some extent, the degree of cutaneous reaction in porphyria may be proportional to the concentration of porphyrins in the tissues and to the kind of porphyrin that is concerned, as well as to the nature and concentration of the light source and the effect of its cumulative action. Photosensitivity is prominent in cases in which porphyrins are injected experimentally into the skin and in cases of congenital porphyria, but it is rarely a feature in cases of so-called acute porphyria. Our first case presented features of both the chronic and the acute phase of porphyria; hence it is difficult to believe that these phases are two distinct diseases of different etiology in respect to the fundamental alteration in the metabolism of the porphyrins.

One may speculate as to the role of the liver in the pathologic physiology of the skin in porphyria. The liver frequently is involved in acute porphyria. The changes in the skin in chronic porphyria may be influenced by the abnormal porphyrins which are produced when the liver is damaged by such a toxin as alcohol, for example; on the other hand, such a damaged liver may also serve to inhibit or destroy certain protective enzymes which are essential in the skin for the prevention of reactions of photosensitivity.

The chief protection of the skin against light is probably the keratin layer, but the value of pigment cannot be dismissed summarily. The decolored skin in vitiligo, for instance, is particularly susceptible to light, and in congenital porphyria in cattle it is the white skin that manifests the photosensitive reaction. The production of pigment in the human skin, in cases of chronic porphyria, is probably a late effect and represents an effort to protect the underlying tissues from penetrating radiation.

In chronic porphyria milia occur in the areas of skin that have been affected by light. They represent invaginated sebaceous accretions, which may occur in normal skin about the eyelids and the genitalia or in scarred skin in diseases, such as pemphigus or epidermolysis bullosa, or in old burns.

In recent years, physicians have become increasingly aware of the importance of the subject of porphyria. If careful search were made of members of families in which isolated cases of manifest porphyria occur, it is reasonable to suppose that a reservoir of cases of latent porphyria would be uncovered.

SUMMARY

The cutaneous reactions of porphyria are discussed in a report of 3 cases in which the disease first became manifest in adult life by means of these symptoms. In each case chronic alcoholism, as well as hepatic dysfunction, may have been a precipitating factor. The syndrome under consideration represents the tardive phase of congenital porphyria, with essentially benign and chronic symptoms, although in 1 case the characteristic clinical and laboratory features of so-called acute porphyria occurred. Quantitative analysis of the urinary porphyrins is presented.

The Mayo Clinic.

ABSTRACT OF DISCUSSION

DR. MICHAEL H. EBERT, Chicago: The excellent presentation of Dr. Brunsting and Dr. Mason illustrates how the careful study of an apparently insignificant cutaneous condition may lead one into fields of internal medicine, of biochemistry and of genetics.

To those who had occasion to look into the literature some years ago, porphyrin was synonymous with hematoporphyrin, which was believed to activate light sensitization in many cases of hydroa. The chemistry of the porphyrins has been intensively studied in the last fifteen years. It is now known that hematoporphyrin is an artificial product of the laboratory and does not exist in the human body.

The porphyrin ring, which is made up of four pyrrole rings bound together by methylene radicals, seems to be of fundamental importance in living things. As a metal complex with iron it forms hemoglobin; with magnesium it produces chlorophyll, and it is the basis of cytochrome C.

Normally, small amounts of coproporphyrin, from 0.4 to 0.5 mg., are excreted daily in the feces and urine. This excretion may be appreciably increased by diverse pathologic conditions, such as high fever, chronic alcoholism, hepatic disease, pernicious anemia, sicklemia or hemolytic jaundice; by poisoning, such as that with lead, a sulfonamide drug, cinchophen or arsphenamine, or by cutaneous conditions, such as pemphigus vulgaris, exfoliative dermatitis, the erythroderma of lymphoblastoma or extensive burns and ulcerations.

The appearance of uroporphyrin in the urine is always pathologic and is evidence of a defect of pyrrole metabolism. This tendency to excrete abnormal kinds and amounts of porphyrin is inherent and familial. It is frequently latent. When activated by some unknown agent it may precipitate acute gastrointestinal symptoms, neuritic pain, paralysis and mental symptoms. This is the type of acute porphyria of great interest to the internist.

In other instances this activation of latent porphyria may result, as Dr. Brunsting has shown us, in cutaneous manifestations, with or without the gastrointestinal and nervous manifestations of the acute type. The cutaneous manifestations are sensitivity to light, increased vulnerability to trauma, hyperpigmentation, formation of milia, and, at times, hypertrichosis. The resemblance to epidermolysis bullosa is striking but not fundamental, according to Dr. Brunsting.

The relation of hydroa aestivale and hydroa vacciniforme is closer to porphyria, especially to the type with early onset and pathologic porphyria, which has been included under the category of congenital porphyria.

Studies of this rare manifestation of porphyria have been recorded from various parts of the world. We are indebted to Dr. Brunsting for calling our attention to it again and for emphasizing that elaborate equipment is not necessary for its recognition.

Qualitative determination of abnormal amounts and kinds of porphyrin in the urine is within the scope of the ordinary hospital laboratory. It is to be emphasized, however, that the excretion may vary from day to day, so that several examinations may be necessary to rule out this condition.

The mechanism of the production of the bullous lesions through the interaction of sunlight and porphyrin is not understood. It is evidently quite different from the photodynamic action of porphyrin injected into the skin experimentally and activated by the appropriate wavelengths of from 3,000 to 4,500 angstrom units. The histologic changes resembling senile elastosis suggest that the action is a much slower one and at a much deeper level.

Finally, it must be emphasized that there is no evidence of this rare disturbance of pyrrole metabolism in the ordinary examples of sensitization to light, such as lupus erythematosus, pellagra, urticaria solaris and summer prurigo.

I am sure we are all stimulated by Dr. Brunsting's report.

DR. DONALD M. PILLSBURY, Philadelphia: This study of Dr. Brunsting's is a particularly fine example of a collaborative effort between a clinician and a scientist working in a difficult field, in which neither the scientist nor the clinician alone could accomplish a great deal.

I should like to report briefly preliminary observations made by Dr. Lawrence Katzenstein, working in the Department of Dermatology and Syphilology at the University of Pennsylvania, in which he found that diphenhydramine hydrochloride (beta-dimethylaminoethylbenzohydryl ether hydrochloride; benadryl®) will protect mice against the lethal effects of hematoporphyrin, which, as has been pointed out, is not a naturally occurring porphyrin in the human body.

This observation is not entirely original with Dr. Katzenstein. Unfortunately, the antihistaminic drugs must be given in extremely large doses, much more than would be feasible clinically, but at least the observation furnishes a possible lead to the treatment of these patients. I do not believe that such patients with disorders of porphyrin metabolism are particularly rare.

DR. H. J. TEMPLETON, Oakland, Calif.: Ten or fifteen years ago, Dr. Lunsford and I prepared a paper which we felt was fairly good in those days, but which in the light of Dr. Brunsting's paper seems elementary.

Our paper was built around 2 patients, 1 of whom exhibited several things of interest. A young girl was referred to us because of severe dermatitis. Then acute abdominal pain appeared, with somnolence; she went into coma; porphyrins were demonstrated in the urine, which was burgundy red, and death occurred.

This was obviously a typical case of acute porphyria, but it was of interest because of the dermal involvement, which does not generally occur in acute porphyria.

The next case was that of a young woman. Her case was of interest because she did not fit exactly into any group. She had light-sensitive lesions of the face and of the neck and reddish urine with porphyrin present. She did not become seriously ill, but she had a number of episodes of the variety described.

Stimulated by these 2 cases, we studied the urine of some university students for the presence of porphyrins. We took a number of students with acne who were due to receive ultraviolet light for chronic acne, and with the help of chemists and physicists the urines were examined before the patients were given treatment with the ultraviolet rays. No porphyrin was found in the urines at that time.

We then exposed the upper half of these patients' bodies to brisk erythema doses of ultraviolet light and, after that exposure, spectroscopic examination demonstrated porphyrin in their urines. At about that same time we had a great number of patients with a rather acute type of pityriasis rosea. We examined the urines of these patients for porphyrin and found it present (prior to ultraviolet ray therapy). This observation caused us to believe that the intense stimulation of the dermis and epidermis by the severe pityriasis rosea had produced secondary, symptomatic, porphyria.

We did not understand the significance of this finding at that time, nor do we understand it now. Dr. Brunsting has told me that he feels that we were observing an intensification of physiologic porphyria.

Dr. Louis A. Brunsting, Rochester, Minn.: In porphyria there is considerable variation from time to time in the amounts of abnormal porphyrins that are excreted, and the factors which govern this are not clearly understood. The discovery of porphyria in a certain herd of cattle in South Africa, as reported by Rimington and others, offers a fertile field for the study of this disease. In certain of these animals, a photosensitive reaction occurred in patches of skin that were colored white. For the most part, the so-called photosensitive diseases of human beings, such as hydroa, urticaria solaris and lupus erythematosus, are not concerned with a disturbance of porphyrin metabolism.

EHLERS-DANLOS SYNDROME

A Clinical and Genetic Study

STURE A. M. JOHNSON, M.D.
MADISON, WIS.
AND
HAROLD F. FALLS, M.D.
ANN ARBOR, MICH.

THE PAUCITY of the literature on the Ehlers-Danlos syndrome in all fields except pediatrics and dermatology would make one believe that the condition has been arrogated by members of these two groups. It seems, however, that the syndrome should have been recognized and emphasized by others. For instance, the orthopedist should have been recording the joint symptoms; the surgeon, the friability of the skin; the roentgenologist, the roentgenologic findings; the pathologist, the tissue changes; the internist, the ecchymoses and hemorrhages, and the geneticist, the familial characteristics. The syndrome, according to Ronchese [1] is characterized by (1) hyperlaxity and hyperextensibility of the joints, (2) hyperelasticity and hyperlaxity of the skin and (3) friability and fragility of the skin and blood vessels, with breaking, splitting and formation of hematomas and pseudotumors subsequent to the slightest trauma. The severity of these characteristics may vary among different persons and in sibships. In some families in which 1 or more members have all the characteristics of the Ehlers-Danlos syndrome other members may have one or two of the characteristics. A few authors have described persons in the latter group as having a forme fruste state of the Ehlers-Danlos disease.

Support of this research was provided in part by the Horace H. Rackham School of Graduate Studies.

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Meeting of the American Medical Association, Chicago, June 24, 1948.

From the Department of Dermatology and Syphilogy of the University of Michigan Medical School, service of Dr. Udo J. Wile and Dr. Arthur C. Curtis, and from the Department of Human Heredity of the Laboratory of Vertebrate Biology, University of Michigan.

1. (*a*) Ronchese, F.: Dermatorrhexis, with Dermatochalasis and Arthrochalasis (So-Called Ehlers-Danlos Syndrome), Am. J. Dis. Child. **51**:1403 (June) 1936. (*b*) Dermatorrhexis (Ehlers-Danlos Syndrome) Urol. & Cutan. Rev. **47**:581, 1943.

HYPERLAXITY AND HYPEREXTENSIBILITY OF THE JOINTS

This characteristic (arthrochalasis; laxitas articularis) may be a source of enjoyment to the patient when he demonstrates his double jointedness, or it may cause him considerable discomfort in walking, writing or doing skilled acts. The disturbance in the joints may be noted when the child starts to walk. It is particularly obvious if the changes of the knee and ankle joints allow much subluxation. In such a situation climbing stairs, running and playing games have to be done in moderation, if at all. Dislocations, sprains, ecchymoses and gaping lacerations result from stumbling and falling caused by joint instability. In some cases the condition has even been diagnosed as myotonia congenita [2] because of the patients' waddling gait or inability to walk or run fast. When extension of the knees is pronounced the person may stand with a tabetic posture.[3] In the shoulder there may be sufficient subluxation for the person to dislocate and replace it with only moderate discomfort.[4] Dislocation of the shoulder may follow putting on a coat.[5]

The metacarpophalangeal joints may show such hyperlaxity and hyperextensibility that the person can touch by extension the dorsum of the wrist with the finger tips. Some can extend the thumb so that it easily touches the wrist. Dorsal flexion is almost as easy as palmar flexion. Often these people can disarticulate the metacarpophalangeal and metatarsophalangeal joints by a pulling traction, on release of which the joints fall back into place with a snap.[6] Congenital bilateral radioulnar synostosis of the first degree has been noted. In

2. (*a*) Schubert, P.: Cutis laxa, Zentralbl. f. Haut- u. Geschlechtskr. **16**:162, 1925. (*b*) Smith, C. H.: Dermatorrhexis (Ehlers-Danlos Syndrome), J. Pediat. **14**:632, 1939.

3. (*a*) Margarot, J.; Deveze, P., and Coll de Carrera: L'hyperlaxité familiale de la peau et des articulations (syndrome de Danlos), Montpellier méd. **3**:133, 1933. (*b*) Hyperlaxité cutanée et articulaire (syndrome de Danlos) existant chez trois membres d'une même famille, Bull. Soc. franç. de dermat. et syph. **40**:277, 1933.

4. Sullivan, J. D.: The Danlos-Ehlers Syndrome: Report of Case with Transient Paralysis of Vocal Cord, Arch. Neurol. & Psychiat. **47**:316 (Feb.) 1942. Raybaud, A., and Guidoni, R.: Hyperlaxité ligamentaire et cutanée: Troubles du métabolisme calcique; Maladie d'Ehlers-Danlos, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:738, 1938.

5. Benjamin, B., and Weiner, H.: Syndrome of Cutaneous Fragility and Hyperelasticity and Articular Hyperlaxity, Am. J. Dis. Child. **65**:247 (Feb.) 1943.

6. Schulmann, E., and Lévy-Coblentz, G.: Hyperélasticité cutanée (cutis laxa) et laxité articulaire avec fragilité anormale de la peau et tumeurs molluscoïdes post-traumatiques (syndrome de Danlos), Bull. Soc. franç. de dermat. et syph. **39**:1252, 1932.

1 case there was anterior luxation of the head of the radius, so that it could be voluntarily displaced. This condition existed also for the radiocubital joint. When the metatarsophalangeal joints are involved by the hyperlaxity and hyperextensibility, flatfoot may result. Even third degree pes planus has been noted.[7]

Generalized and bilateral laxity of the temporomaxillary joint, of the cervical vertebrae as well as of other parts of the spine has been reported.[8] The hyperlaxity of the joints may be so pronounced that a person may place the arm behind the back and touch the ears with the fingers[9] or take the heel of the foot and touch the umbilicus.[10] Touching the back with the nape of the neck or touching the knees with the face when standing with the lower extremities in extension may be very easy for some of the affected persons.[11]

The clavicles may be mobile because of loose sternoclavicular articulations or even appear completely independent of the sternum.[3b] In the same case the clavicles were separated by the width of a finger in their habitual position and when the shoulders were thrown back they were separated by the width of 4 fingerbreadths.[3b]

Some affected persons have sustained spontaneous dislocations of the patella which would force them to reduce the dislocation before proceeding.[12]

Congenital dislocation of the hip has been reported in a person with the Ehlers-Danlos syndrome.[13]

HYPERELASTICITY AND HYPERLAXITY OF THE SKIN

The abnormality of the skin (dermatochalasis; laxitas cutis) may be so pronounced that a person can painlessly tent or pull the skin like a rubber sheet for 6 to 8 inches (15 to 20 cm.). On release, the skin immediately returns to its normal position, without rugae or wrinkles.

---

7. Pittinos, G. E.: Ehlers-Danlos Syndrome with a Disturbance of Creatine Metabolism, J. Pediat. **19**:85, 1941.

8. Rocher, H. L.; Petges, G., and LeCoulant, P.: Hyperélasticité articulaire et hyperélasticité cutanée d'origine congénitale dystrophique (syndrome d'Ehlers-Danlos), Rev. d'orthop. **21**:673, 1934.

9. Lowe, J.: Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **32**:1027, 1939.

10. Burrows, A.: Epidermolysis Bullosa with Cutis Hyperelastica, Proc. Roy. Soc. Med. **25**:1319, 1932.

11. Poumeau-Delille, G., and Soulié, P: Un cas d'hyperlaxité cutanée et articulaire avec cicatrices atrophiques et pseudo-tumeurs molluscoïdes, (syndrome d'Ehlers-Danlos), Bull. et mém. Soc. méd. d.hôp. de Paris **50**:593, 1934.

12. Ehlers, E.: Cutis laxa, Neigung zu Haemorrhagien in der Haut, Lockerung mehrerer Artikulationen, Dermat. Ztschr. **8**:173, 1901.

13. Debré, R., and Semelaigne G.: A propos de la maladie d'Ehlers-Danlos chez le nourrisson, Bull. et mém. Soc. méd. d.hôp. de Paris **57**:849, 1938.

This is the type of elasticity of the skin found in a cat or a dog. Tobias [14] said that in this condition the skin can be picked up in folds like accordion plaits. In 1 reported case the skin was so elastic that it could be wound around the finger one and a half times.[12] In another, the patient could pull the skin over the sternum up to his mouth.[15] Elasticity may be limited to a few areas of the body, to one side of the body [16] or to mucous surfaces, particularly of the mouth and the tongue.[17] The skin seems to be more elastic over the bony prominences of the body, where normally it is fixed or bound. Though no pain is usually associated with the condition, a few persons have noted an intensely disagreeable sensation when the body was rubbed with a towel.[18] Hypesthesia has been described.[19] It is interesting to note that the skin of these people does resist progressive distention, so that abdominal striae do not occur even after the delivery of a 4,500 Gm. baby.[17]

The skin itself has a peculiar feel. When it is palpated, one notices a thinness and an absence of the adipose panniculus which are similar to conditions observed in the eyelids of normal persons. Roca and Loiacono [20] thought the skin felt like a rubber band. Others have likened the feel of the skin to that of the peeling of a baked apple.[12] Smith [2b] was impressed by the peculiar velvety and putty-like feel of the skin.

FRAGILITY OF THE SKIN

Cutaneous fragility (dermatorrhexis; fragilitas cutis) is a disturbing factor to the patient as well as to the surgeon. A slight bump or glancing blow may result in a gaping wound or skin flap. A small cut, laceration or incision of the skin may become appreciably wider, longer and deeper as a result of the edges' pulling away from the wound because of the elasticity of the cutis. Lacerations may be multiple and occur often because of the unstable joints, which allow stumbling and falling. Ordinary sutures tend to pull out, so that skin clips and bridges of

14. Tobias, N.: Danlos Syndrome Associated with Congenital Lipomatosis, Arch. Dermat. & Syph. **30**:540 (Oct.) 1934.

15. Murray, J. E., and Tyars, M. E.: A Case of Ehlers-Danlos Syndrome, Brit. M. J. **1**:974, 1940.

16. Gordon, H.: Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **35**:263, 1942.

17. Dreyfus, G.; Weill, J.; Martineau, J., and Mathivat, A.: Un cas de maladie d'Ehlers-Danlos, Bull. et mém. Soc. méd. d.hôp. de Paris **52**:1463, 1936.

18. Barber, H. S.; Fiddes, J., and Benians, T. H. C.: The Syndrome of Ehlers-Danlos, Brit. J. Dermat. **53**:97, 1941.

19. Danlos Syndrome, presented from clinics of Washington University School of Medicine, Arch. Dermat. & Syph. **40**:137 (July) 1939.

20. Roca, C. A., and Loiacono, G. J.: Sindrome d'Ehlers-Danlos, Semana méd. **49**:887, 1942.

adhesive tape have been used to close the gaping wounds. Many patients know about this tendency and will advise the surgeon who is not acquainted with the condition. The skin is so vulnerable to slight trauma in some persons that T-shaped splitting of the skin requiring six stitches has occurred after the twisting of the wrist.[21] In 1 child 285 stitches had been placed because of frequent lacerations suffered by the child from stumbling and falling. At this stage the father lost count.[22]

Unless the edges have been proximated by a surgical procedure the lacerations are slow to heal. The resulting scars, which are a prominent feature of the syndrome, may be linear, wrinkled, papyraceous or criss-crossed. These may bulge or balloon out from the normal skin like a hernia or pseudotumor. The thin, atrophic skin of the scar may be alternately achromic and hyperpigmented, with some fine telangiectasia. The scarring is usually most prominent over the bony prominences subject to trauma, like the forehead, elbows, knees and tibial surfaces. The scars are characterized further by not being adherent to the subcutaneous tissues, by not being firm like a keloid and by being reducible like a hernia.

Bleeding is not a prominent feature of the wounds, since the edges of the wound retract because of the elasticity of the skin and compress the ends of the severed blood vessels. In spite of this tendency, van Aardenne[23] and others[24] have reported instances in which persons have bled profusely from trivial trauma. Profuse bleeding has occurred in patients after tonsillectomy and tooth extraction, though bleeding times of 2 minutes and clotting times of 90 seconds, with normal platelet counts, have been present.

Associated with the friability of the skin is vulnerability and fragility of the blood vessels. Large hematomas may occur after blows which in themselves are not sufficiently hard to break the surface of the skin. Frequent trauma over the achilles tendon, caused by the wearing of the shoes, may result in changes which have been likened to angiomas. Hematomas have been known to follow mere stretching of the skin to demonstrate its hyperelasticity.[25] Ecchymoses from pressure on the

21. Bolam, M.: A Case of Ehlers-Danlos Syndrome, Brit. J. Dermat. **50**:174, 1938.

22. Brown, A., and Stock, V. F.: Dermatorrhexis: Report of a Case, Am. J. Dis. Child. **54**:956 (Oct.) 1937.

23. van Aardenne, J.: Dermatorrhexis with Dermatochalasis and Arthrochalasis (Danlos-Ehlers Syndrome), Maandschr. v. kindergeneesk. **8**:187, 1939.

24. Gordon.[16] Capurro, R.: Cutis laxa, hematomas, atrofias cutáneas, hipotonía muscular, laxitud articular, Arch. latino-am. de pediat. **20**:713, 1926. Thurman, F. M.: Ehlers-Danlos Syndrome, Arch. Dermat. & Syph. **40**:120 (July) 1939.

25. Smith.[2b] Benjamin and Weiner.[5]

arm [26] and from performance of the Rumpel-Leede test have occurred.[27] The presence of recent hematomas and of resolving hematomas gives a characteristic color of reds, greens, yellows and blacks to the papyraceous, tumor-like scars. Raisin-like appearance of the skin has been a frequent description. Absorption of the hematomas may be linked with a rise in temperature.[21] Numerous studies of the blood, with respect to bleeding time, coagulation and thrombocyte counts, for example, have failed to demonstrate abnormalities of the blood in these people. Ecchymoses occurring particularly at the menstrual periods have been noted.[17] Bullous lesions rather than hemorrhagic lesions have also been reported.[28]

Spheroids or small cystlike tumors have been found in the subcutaneous tissues of so many of the people having the Ehlers-Danlos syndrome that some authors think that these tumors should be considered a feature of the condition. The bodies are freely movable, like bird shot, in the subcutis. They are round, may vary in size from that of a pea to that of a hazlenut and occur in the skin of the extremities and also of the buttocks.[14] Weber and Aitken [27] stated that these spheroids were not lipomas but represented budlike development of freely movable nodules from the subcutaneous fat which, by gradual thinning and atrophy of their pedicles, lose their blood supply and become more or less free bodies in the loose subcutaneous tissues. In time they become oil-containing cysts with thickened fibrous—even calcareous—walls. No doubt the spheroids are associated with the friability of the skin and are due to trauma.

Attention has been called to the prominent, widely spaced eyes, wide bridge of the nose and lack of subcutaneous tissue over the face, particularly in the cheeks, of many of these patients. The frequent occurrence of epicanthic folds in these people has also been noted.[29] Other reported abnormalities over which there has been some disagreement as to their importance in the syndrome are the notched lower incisors,[3b] absent

26. Launay, C.: Syndrome d'Ehlers-Danlos chez un garçon de onze ans associé à une arriération mentale, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:709, 1940.

27. Weber, F. P., and Aitken, J. K.: Nature of the Subcutaneous Spherules in Some Cases of the Ehlers-Danlos Syndrome, Lancet **1**:198, 1938.

28. Gilbert, A.; Villaret, M., and Bosviel, G.: Sur un cas d'hyperélasticité congénitale des ligaments articulaires et de la peau, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:303, 1925.

29. (*a*) Benjamin and Weiner.[5] (*b*) Shaw, A. B., and Hopkins, P.: A Case of a Boy, Aged 7, Showing (*a*) Double-jointedness, (*b*) Dermatolysis ("Elastic Skin") with Great Friability of the Skin and Excessive Tendency to Bruising and (c) Multiple Subcutaneous Tumors on the Limbs (?Fibromata, ?Neuromata), Proc. Roy. Soc. Med. (Clin. Sect.) **6**:20, 1912-1913.

upper incisors,[30b] acrocyanosis,[30] microdontia,[31] mental retardation,[31] supernumerary teeth, clubfoot [32] and lipomatosis.[14] Pronounced rugosity of the scalp has been associated with the syndrome.[19]

For the most part roentgenologic studies of long bones, skull and joints have shed no light on the etiology of the syndrome.[33] Roentgenograms showing decided hyperextensibility of the joints appear in several articles.[34] There are isolated findings of congenital bilateral radioulnar synostosis,[9] small lymph spaces of pinhead size in bones of the hand,[17] transverse lines of long bones and delayed cranial ossification and closing of fontanels.[35] In the roentgenologic examination of 1 child having curvature of the back, the bones were seen to be generally translucent, with normal epiphyseal development. The most recent roentgenologic study of patients with the Ehlers-Danlos syndrome was done by Holt,[34c] who used for his thesis the roentgenologic findings in the 2 cases here reported. Holt was particularly interested in the roentgenologic findings of the subcutaneous spheroids which our patients had (fig. 1). He stated that this manifestation of the syndrome was of particular importance to the roentgenologist and that Smith [2b] and Bolam [21] had mentioned finding calcified areas in soft tissues. According to Holt, roentgenologically it is difficult to differentiate the calcified nodules of Ehlers-Danlos syndrome from the phleboliths in hemangiomas and to differentiate the pseudotumors of the syndrome from the irregular tumor masses of sizable angiomas. He stated that the angiomatous phleboliths could be differentiated from the spheroids by their tendency to involve the deeper soft tissues, greater variation in size, irregular outline and multiple concentric strata of calcium. He remarked further that the larvae of parasites may calcify in muscles and may vaguely resemble those calcifications seen in the Ehlers-Danlos syndrome, and also he stated that the commonly seen soft tissue calcifications can be differentiated by their solitariness or by their occurrence in amorphous fashion.

The only pathologic change reported in the epidermis has been wrinkling due to contraction of the elastic network in the underlying corium.

---

30. Dreyfus, Weill, Martineau and Mathivat.[17] Weber, F. P.: Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **32**:1026, 1939.

31. Cathala, J.: Cutis laxa et syndrome d'Ehlers-Danlos, Arch. de méd. d. enf. **40**:107, 1937.

32. Hallopeau, H., and Léspinay, M.: Sur un cas de xanthome tubéreux et en tumeurs juvénile offrant les caractéres du xanthome diabétique, Bull. Soc. franç. de dermat. et syph. **17**:283, 1906.

33. Tobias, N.: Danlos' Syndrome, Associated with Congenital Lipomatosis, Arch. Dermat. & Syph. **40**:135 (July) 1939.

34. (*a*) Dreyfus, Weill, Martineau and Mathivat.[17] (*b*) Roca and Loiacono.[20] (*c*) Holt, J. F.: The Ehlers-Danlos Syndrome, Am. J. Roentgenol. **55**:420, 1946.

35. Debré and Semelaigne.[18] Shaw and Hopkins.[29b]

Various changes in the elastic fibers of the corium have been observed. Smith [2b] and Pittinos [7] found them thicker and larger than those of the normal corium and not broken up like the normal fibers. Ronchese [1a] noted that the elastic fibers occurred as a dense reticulum of the coarse and fine wavy fibrils. Excessive amounts of elastic elements in whorls and clumps have been seen by many.[36] Williams [37] and Pautrier,[38] who found the elastic tissue normal, and Brown and Stock,[22] who found the elastic tissue fibers diminished, are exceptions. Tobias [14] reported that the elastic fibers mixed diffusely with the collagen fibers and that they were more numerous, delicate and branching than is normal.

Diminution in the collagen of the corium has been reported by many.[39] Hypertrophy and torsion of the collagenous tissue has been

Fig. 1.—A prominent collection of nodules may be seen over the insertion of the deltoid muscle. Dense outer margins and relatively radiolucent centers characterize most of the lesions.

36. (*a*) Barber, Tiddes and Benians.[18]. (*b*) Stillians, A. W., and Zakon, S. J.: Cutis Laxa (Cutis Hyperelastica) Arch. Dermat. & Syph. **35**:342 (Feb.) 1937. (*c*) Navarro Martin, A., and Aguilera Maruri, C.: Un caso de cutis laxa y lesiones atróficas de tipo eritromiélico, Actas dermo-sif. **25**:126, 1932. (*d*) Miguet, A.: Le syndrome d'Ehlers-Danlos, Thesis, Paris, Louis Arnette, 1933. Weber, F. P.: Chalasodermia or "Loose Skin" and Its Relationship to Subcutaneous Fibrous or Calcareous Nodules, Urol. & Cutan. Rev. **27**:407, 1923.

37. Williams, A. W.: Cutis Laxa, Monatsh. f. prakt. Dermat. **14**:490, 1892.

38. Pautrier, M.: Note histologique sur un cas de cutis elastica, avec pseudotumeurs aux génaux et aux caudes, prèsenté par M. Danlos, Bull. Soc. franç. de dermat. et syph. **19**:72, 1908.

39. (*a*) Smith.[2b] (*b*) Tobias.[14c] (*c*) Weber.[36e] (*d*) Williams.[37] (*e*) Ormsby, O., and Tobin, W. W.: Cutis Hyperelastica, Arch. Dermat. & Syph. **38**:828 (Nov.) 1938. (f) Burrows, A., and Turnbull, H. M.: Cutis Hyperelastica (Ehlers-Danlos Syndrome), Brit. J. Dermat. **50**:648, 1938.

seen.[40] Myxomatous changes were noted by Bolam.[21] Tobias [14] found that the collagen fibers had assumed fine-meshed, well separated fibrillar structures instead of the normal loose-woven but thick-bundled variety. Coe and Silvers [41] saw wavy arrangement of all elements and increase in both elastic and connective tissue bundles. Rambar [42] found appreciable new formation of connective and elastic fibers. Increase in muscular tissue [43] and no change in the muscle fibers have been observed.[44]

The blood vessels have been found to be irregular in their course and winding. Rambar [42] reported thick-walled vessels with occasional thrombi in the smaller arteries, while Tobias [14] found large-lumened blood vessels with thin, almost insufficient-looking, walls.

On biopsy of the spheroid bodies ordinary fat and mucoid material have been seen enclosed in fibrous capsules.[45] The capsules have contained mostly collagen fibers, with a few scattered elastic fibers and occasional calcium deposits.

Foreign body giant cells have been numerous in certain specimens. Ronchese [18] saw scattered nodules composed of large fusiform cells, polyhedral mononuclear cells and large multinucleated giant cells with an abundance of acidophilic cytoplasm. Barber [18] found clear spaces in the giant cells, as though fatty bodies had been present. These giant cells were grouped in the form of glandular lobules. Scolari,[46] in a study of the histology of the molluscoid pseudotumors, found proliferation of the connective tissue, with large numbers of vessels in it producing angiofibromatous growths. In this tissue, foci of fatty degeneration appeared. Cystic formation due to splitting of the collagen fibers was also seen. Though tissue studies of the capsule, the ligaments of the lax joints and the hollow viscera have not been made, Tobias [33] and Ormsby [39e] by analogy assumed that there may be elastic tissue fiber disturbances.

---

40. Navarro Martin and Aquilera Maruri.[36c] Reyn, A.: Cutis Laxa, Hospitalstid. **76**:961, 1933.

41. Coe, M., and Silvers, S. H.: Ehlers-Danlos Syndrome (Cutis Hyperelastica), Am. J. Dis. Child. **59**:129 (Jan.) 1940.

42. Rambar, A. C.: Ehlers-Danlos Syndrome, J. Pediat. **12**:592, 1938.

43. Ormsby and Tobin.[39e] Unna, P. G.: The Histopathology of the Diseases of the Skin, translated from the German with the assistance of the author by N. Walker, New York, Macmillan & Co., 1896.

44. Smith.[2b] Pittinos.[7]

45. (*a*) Tobias.[14] (*b*) Barber, Tiddes and Benians.[18] (*c*) Weber and Aitken.[27] (*d*) Weber, F. P., and Aitken, J. K.: Subcutaneous Movable Spherules in the Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **31**:553, 1938.

46. Scolari, E.: The Ehlers-Danlos Syndrome: Histology of the So-Called Molluscoid Pseudo-Tumours, Gior. ital. di dermat. e sif. **78**:577, 1937.

Little is known concerning the etiology of the Ehlers-Danlos syndrome, except that the condition is congenital. Whether prematurity is the cause or the effect of the syndrome is not known. In several cases in which only 1 child in a family has expressed the syndrome, the child has been a premature baby.[47] Consanguinity, the parents' being first cousins, was considered a factor in the cases of Weber and Aitken [45d] and of Ronchese.[1a] There are many pedigrees available to show that the disease is often familial (table 1). The syndrome has been regarded by Benjamin and Weiner [5] and others [48] as a congenital, constitutional and developmental mesenchymatous dysplasia. These authors expressed the feeling that the same unknown disturbance of the mesenchyme responsible for the anomalies of the skin, which is of ectodermal origin,

TABLE 1.—*Reports of Pedigrees in the Literature*

Author	Generations	Affected Persons: Male	Affected Persons: Female	Normal Sibs
Margarot and associates [3b]	2	3	..	3
Burrows (14)	2	1	2	..
Murray and Tyars [15]	3	3	2	1
Barber and associates [18]	2	2	..	..
Roca and Loiacono [20]	1	2	..	..
Gilbert and associates [28]	2	..	4	5
Stuart [56]	4	3	8	6
Ormsby and Tobin [39a]	3	3	1	2
Cole and Silvers [41]	4	3	1	6
Kopp [49]	2	2	..	..
Klebenav, G. J.: Vestnik venerol. i dermat. **6**:636, 1937	3	5	6	11
Von Kopp, cited by Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933	3	4	7	5
Berggreen, P.: Dermat. Wchnschr. **104**:374, 1937	3	3	1	7
Goldsmith [57]	2	1	1	..
Wiener, K.: Arch. f. Dermat. u. Syph. **148**:569, 1924-1925	3	5	5	5
Schulmann, E., and Lévy-Coblentz, G.: Bull. Soc. franç. de dermat. et syph. **40**:380, 1933	2	..	2	..

causes the changes in the capsules and ligaments of the joints, which are of mesodermal origin. They observed further that, although the teeth have been reported affected, no involvement of the nails and the hair has been reported.

Brown and Stock [22] stated the belief that the underlying cause was a congenital defect in the collagen fibers, which did not possess their normal tensile strength and thus allowed the skin to be stretched beyond its normal limits. As an etiologic agent, disturbances in calcium metabolism have been mentioned by some [18] and their role doubted by others.

47. (*a*) Ronchese.[1a] (*b*) Benjamin and Weiner.[5] (*c*) Shaw and Hopkins.[29b] (*d*) Rambar.[42] (*e*) Skeer, J., and Kaplan, A. A.: Ehlers-Danlos Syndrome, Arch. Dermat. & Syph. **42**:450 (Sept.) 1940. (*f*) Sézary, A.; Azérad, E.; Miget, A. and Deparis: Syndrome d'Ehlers-Danlos, Bull. Soc. franç. de dermat. et syph. **40**:1287, 1933.

48. Hirszfeldowa, H., and Sterling, W.: Konstitutionelle Mesenchymosen; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **16**:803, 1924.

Kopp [49] expressed the feeling that atavism was a factor in the development of the condition. The endocrine system has been implicated by Burrows [10] and Dobrosworskaya.[50]

Many [51] have expressed the opinion that the Ehlers-Danlos syndrome is related to von Recklinghausen's condition (neurofibromatosis). On the other hand, Weber [52] stated the belief that the syndrome was a distinct entity and should not be associated with von Recklinghausen's condition, epidermolysis bullosa, acrodermatitis chronica and idiopathic striae atrophicae.

Treatment of the syndrome has been limited more or less to protection of the person. Leather shin guards,[53] high boots and ankle supports [22] have been recommended. In the hands of some physicians, compression bandages over the hematomas have resulted in rapid

Fig. 2.—Typical scars of the forehead and the wide nasal bridge may be observed.

absorption without tumor formation.[54] Orthopedic surgery is indicated to correct joint function when there is handicap due to laxity or perma-

49. Kopp: Demonstration zweier Fälle von "Cutis Laxa," München. med. Wchnschr. **35**:259, 1888.

50. Dobrosworskaya, N. W.: Cutis hyperplastica; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **15**:437, 1924.

51. Tobias.[14] Roca and Loiacono.[20] Bielschowsky, F.: Beitrag zur Klinik und Pathologie der Lipatrophia circumscripta (Cutis laxa), Deutsches Arch. f. Klin. Med. **166**:96, 1930.

52. Weber, F. P.: The Ehlers-Danlos Syndrome, Brit. J. Dermat. **48**:609, 1936.

53. Benjamin and Weiner.[5] Rambar.[42]

54. Ormsby and Tobin.[39e] Rambar.[42] Skeer and Kaplan.[47e]

Fig. 3.—The degree with which the shoulders could be approximated because of hyperlaxity of the joints is exhibited.

Fig. 4.—Hyperextensibility of the thumb, hyperelasticity of the skin, scars of the arm and pseudotumors of the elbow are revealed in this photograph.

nent dislocation.[55] Smith [2b] cut down injuries of the skin to a minimum in 1 of his patients by having the patient put on weight. He expressed the belief that the improvement was due to increased deposition of fat in the subcutaneous tissues.

REPORT OF CASES

CASE 1.—V. M. E., a 16 year old white school girl, was referred to the dermatology clinic by the department of orthopedics (service of Dr. Carl Badgley) because of a peculiar scarring of the face and the extremities. The patient stated that, for as long as she could remember, slight injury to the skin had resulted in large, gaping wounds. These lacerations would heal slowly, leaving scars which were inelastic, soft, pigmented or depigmented and wrinkled. Often, instead of a laceration, there would develop large bruises which resolved slowly. In some parts of the extremities a constant blue to purple was noted because of repeated hematomas. This coloring was particularly noticeable near or in areas where scars were already present. Fresh, gaping wounds did not hemorrhage, though the wound was large. There was no history of abnormal bleeding following the extraction of teeth or at the menses. The edges of the lacerations in many instances were brought together by skin clips, since sutures would tear out. The patient noted that her skin could be stretched more than could that of her friends. For most of her life she had noted difficulty in walking or in running without stumbling. There was a feeling of insecurity in the ankles and the knees. It was the constant stumbling and falling which caused new lacerations, new hematomas and new scars.

The systemic review revealed the presence of recurrent headaches of recent origin. The patient freckled easily and perspired only fairly. She was a premature baby, born after an eight month pregnancy. Lately, pain and swelling had occurred in the left knee.

The physical examination disclosed a temperature of 99 F., a pulse rate of 80, a respiratory rate of 22 and a blood pressure of 120 systolic and 70 diastolic. The patient, though she was not ambulatory, was not acutely ill. The hair was light auburn. The eyebrows and the eyelashes were normal, while the axillary and pubic hair was sparse. The scalp line was high, this fact making the forehead prominent (fig. 2). The eyes were brown. The bridge of the nose was wide. There was a congenital fistula of the left ear. The teeth showed no congenital abnormality. The left knee was swollen and painful to touch and on motion. The clavicles could almost be approximated (fig. 3). The joints of the fingers, wrists, elbows and toes and the right knee could be hyperextended (fig. 4). Pressure on the foot pads made them roll and flatten out like a moccasin. Cranial bossing was present. The skin of the face had a pasty, doughy appearance. There were linear and crosshatched scars on the forehead and the cheeks (fig. 2). On the dorsa of the hands and knuckles were a few linear, wrinkled, pigmented scars. On the elbows and the ulnar aspects of both arms were numerous thin, pigmented, papyraceous scars, which ballooned. On the tibial surfaces, the malleoli and the knees were pigmented, bluish, atrophic, thin, ballooning scars. On each buttock were healed scars. In many of the scars there were hematomas in various stages of resolution. Hematomas were seen elsewhere as well. On the knees and over the achilles tendon the hematomas were literally piled on

55. Taylor, F. R.: The Meekrin-Ehlers-Danlos Syndrome, Urol. & Cutan. Rev. **47**:378, 1943.

each other, tumor-like masses of various colors thus being caused. On palpation of the skin of the arms one could feel numerous small pea-sized, freely movable bodies in the cutis. The skin over the entire body could be stretched or tented for from 3 to 4 inches (7.5 to 10 cm.) (figs. 4 and 5), on release returning immediately to its original position. No pain or hematomas resulted from this stretching. The skin itself had an abnormal feel. It lacked its normal turgor, and it gave one the feeling that his hand was running over a rubber sheet under which there were rubber bands.

Laboratory examination revealed a normal urine and blood. The sedimentation rate was 29 mm. in one hour. The blood type was B, and the reaction in the Kahn serologic test was negative. The inorganic phosphates were 4.5 mg. per hundred cubic centimeters, and the serum calcium, 11.5 mg.; the alkaline phos-

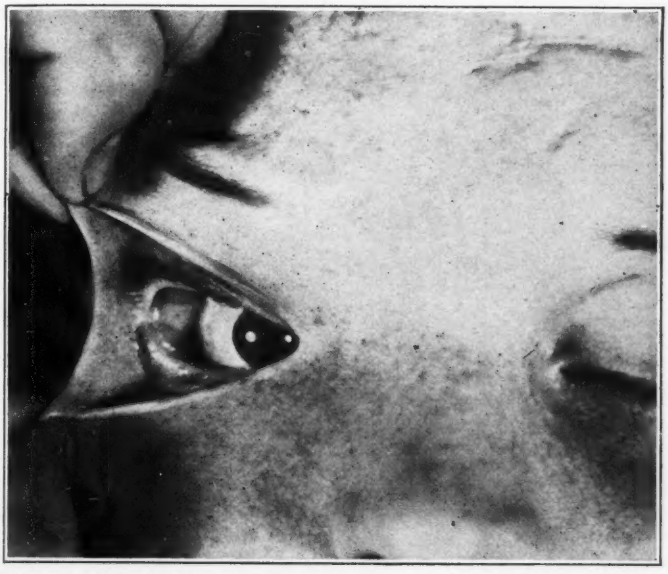


Fig. 5.—Hyperelasticity of the skin, the wide bridge of the nose and the typical scars on the forehead may be seen.

phatase was 5.6 units (Bodansky), and the acid phosphatase, 2.1 units (King-Armstrong). The bleeding time was 1¾ minutes, the clotting time 5 minutes and the prothrombin time 1 minute 10 seconds.

The ophthalmologic examination divulged a nasal epicanthus of each eye. The slit lamp showed in the right eye a small central opacity which appeared to be in front of the anterior Y suture. Few pinpoint opacities were seen laterally. In the left eye was seen a small pupillary remnant. The lens showed small opacities. There were numerous minute cortical opacities.

Roentgenograms of the left knee showed a primary malignant growth of the bone. There were no metastatic lesions.

When a specimen of the tumor of the bone was removed for biopsy it was noted that the skin retracted rapidly and enlarged the incision. Hemostats were

ineffectual inasmuch as the connective tissue would not hold them. When an attempt was made to close the wound after the removal of the biopsy specimen, the sutures placed in the deep tissues pulled out readily. It was necessary to strengthen the skin sutures by using strips of adhesive tape. Later, when the left leg was amputated for an osteochondrosarcoma, the blood vessels did not retract readily and were easily severed by ligatures.

In biopsy of the skin slight perivascular round cell infiltration in the corium was observed. The elastic tissue fibers were increased in number, as was shown

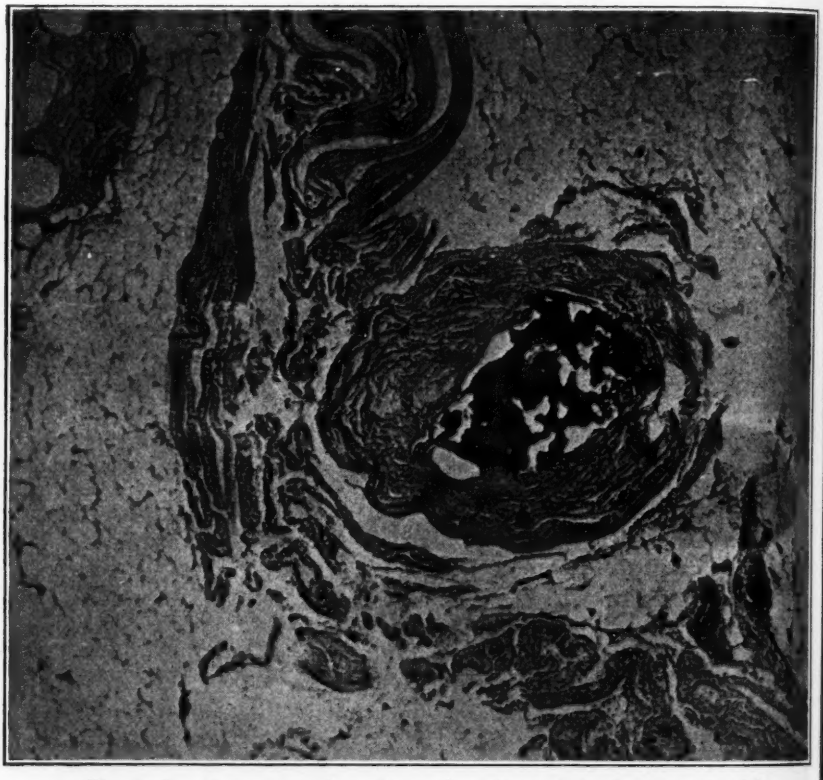


Fig. 6.—In a low power view of a section of a typical subcutaneous nodule, calcified necrotic fat (center) may be observed surrounded by a collagenous fibrous tissue capsule. (Courtesy of Dr. Holt)

by elastic tissue stain. The collagenous fibers were less numerous than usual. There was slight proliferation of the blood vessels of the corium. The scars showed regeneration of the epithelium over connective tissue scars. There were atrophy and necrosis of the voluntary muscle. There were several areas of foreign body giant cell reaction about colorless foreign bodies which had the appearance of glass. These foreign bodies varied in size and shape. The sub-

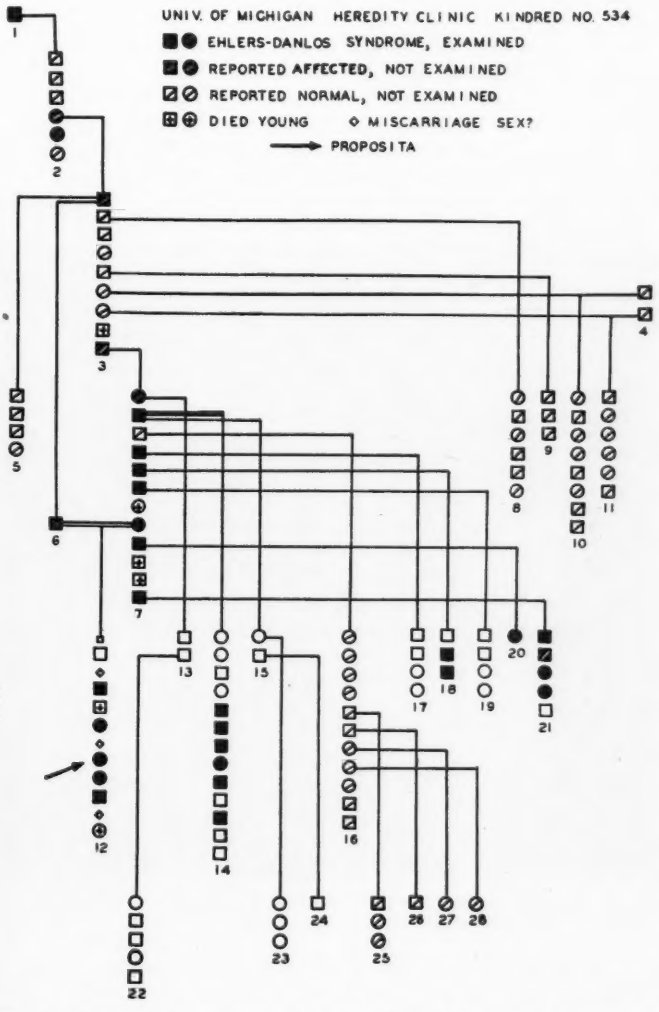

UNIV. OF MICHIGAN HEREDITY CLINIC KINDRED NO. 534
EHLERS-DANLOS SYNDROME, EXAMINED
REPORTED AFFECTED, NOT EXAMINED
REPORTED NORMAL, NOT EXAMINED
DIED YOUNG ◇ MISCARRIAGE SEX?
PROPOSITA

Fig. 7.—The pedigree diagram of kindred 534 differs from the conventional diagram by having the children of a single union arranged vertically rather than horizontally. The sibships are numbered, and a specific person is referred to by means of the sibship number followed by a number denoting his or her position (from top to bottom, the position corresponding to the order of birth) within the sibship. Thus, sib 12-8 is the proposita. Serologic tests of blood and saliva did not reveal any evidence that the legal parents of the sibships studied were not also the biologic parents.

cutaneous nodules showed fat cells within collagenous fibrous capsules of varying thickness. Some of the fat cells were necrotic; others appeared normal. Calcium, when present, was deposited throughout the necrotic fat. Foreign body giant cells were seen occasionally with the necrotic fat (fig. 6).

Case 2.—V. E., aged 18, a sister of V. M. E., was also examined. She stated that her skin (like her sister's) had always been elastic and that slight blows had caused hematomas, gaping wounds and tears. These wounds healed slowly and were prone to ooze but not hemorrhage. Many times, when a laceration occurred in an area where there was an old scar, small, pea-sized, bony, round bodies would

Fig. 8.—Typical scars of the tibial region and the pseudotumors of the knee are shown in the photograph.

drop out on the ground or lie free in the wound. There had been a feeling for a time, before the hyperextensibility of the joints was noticed, that the patient's obesity was the cause of her clumsiness and tendency to fall when running or walking fast. These falls had caused her to fracture her left wrist four times and her right wrist once. Frequent spraining of the wrists and the ankles had occurred. Skin clips had been used to repair some of the lacerations, since ordinary sutures pulled out. The patient was a premature baby, born after 7½ months of pregnancy. She stated that, besides her sister, there were many other members of the family suffering from the same condition (fig. 7).

The systemic review revealed bleeding of the gums, which commonly followed the brushing of the teeth. The menstrual periods started when the

patient was 16, and they have been irregular and painful. Shooting pain between shoulder blades, particularly when the patient sits or lies flat, has been noted. This can be relieved by pressure over the vertebral column.

The physical examination showed a temperature of 98.6 F., a respiratory rate of 20, a pulse rate of 75 and a blood pressure of 120 systolic and 70 diastolic. The patient weighed 159 pounds (72 Kg.) and appeared obese. The hair was auburn. The eyebrows and the eyelashes were normal. There was an epicanthus of each eye. The axillary and the pubic hair was sparse. The forehead was high and the nasal bridge wide. The teeth were normal but carious. There was difficulty in wrinkling the forehead and in squeezing the eyes shut. There was no expression in the face. There were multiple deep scars on the forehead, the cheeks and the chin. Many of these scars were linear and many crisscrossed. Others were V shaped. Those on the chin contained numerous milia. There were many hematomas in various stages of resolution on the extremities and on the buttocks. On the first, second and third knuckles of the left hand and on the second knuckle of the right hand were papyraceous, raised, wrinkled soft scars. These ballooned and were purplish. The palms and the soles were spared, as were the nails. On the left elbow was a large tumor-like mass with many satellite lesions, which were pigmented in browns, yellows, blues and purples. The skin was loose. Freckling of the arms was prominent. There were scars and pseudotumors about the ankles and particularly over the achilles tendons, where the shoes had rubbed. The tibial surfaces were involved. Over the knees were large molluscoid tumors surrounded by smaller tumors with purple pigment and scarring (fig. 8). There were linear and xanthomatous scars on the buttocks. The skin of the whole body was hyperelastic, and it could be stretched without causing pain or hematomas. The labia were found to be very elastic. When the skin about the eyes was stretched one could literally see behind the eye. The fingers and the toes could be hyperextended. The left wrist could be bent back so that the hand almost touched the wrist, while the right wrist was fixed, probably because of old fractures. There was hyperextensibility of the elbows and the knees. The clavicles could be closely approximated. There was tenderness along the whole vertebral column. The skin had a rubbery, doughy feel. In places, freely movable bodies could be felt under the skin. These bodies were particularly numerous on the arms, on the legs between the knees and on the ankles. They were not present in the areas over the knees and the ankles, where the cutaneous lesions were most prominent. On pressure the feet showed a "moccasin foot" deformity. The right breast was much smaller than the left.

Laboratory examination revealed essentially normal urine and blood. The Kahn test for syphilis gave negative reactions.

The roentgenologic examination by Dr. Holt [34c] showed in a single anteroposterior projection of the arms a widely disseminated soft tissue calcification (fig. 1). There were multiple, widespread, ovoid and circular discrete calcium densities varying from less than 1 mm. to 8 mm. in diameter. Localization appeared to be confined to the dermis and the subcutaneous tissues. These densities were seen on the outer aspect of the upper arm and on the extensor surfaces of the forearms. Individually, the subcutaneous calcium deposits had a central zone of relatively increased translucency surrounded by a ringlike shadow of lime salt. Some of the nodules were finely stippled, and a few, entirely homogeneous. The subcutaneous fascial layer appeared unusually thick and, contrasted with the muscular shadows, was of reduced translucency. Anteroposterior and lateral views of both ankles showed similar calcium densities beginning about

4 inches above the ankles and extending up the leg to the knees. The dermal margin posterior to the lower portion of the right leg appeared uneven and slightly pitted. Dr. Holt remarked that the calcium deposits were absent directly over the knees and ankles, where the lesions of the skin were most prominent. Fewer calcifications were seen over the trochanteric regions bilaterally and over the outer aspects of the thighs. The bones and joints did not appear abnormal. A slight degree of pes cavus was present on the right side. A single lateral projection of the skull revealed no abnormality.

FAMILY HISTORY

The earliest known affected person in the family was sib 1-1 (fig. 7). He migrated to Canada from England in the early part of the nineteenth century. His descendants report this man as affected because minor wounds and injuries always took a good deal of time to heal. It was further recalled that his scars remained blue for many months.

Sib 2-4 is claimed to have been affected because of her ability to do unusual physical tricks and acrobatics. She likewise experienced the same difficulty with delayed healing of wounds as did her father. She was recorded to have been large and fleshy.

Sib 2-5 is reported to have had the syndrome because of the presence of large, bluish scars on her knees and elbows and also of very deep pits on the forehead.

Several very large tissue paper–thin scars are recalled by sib 3-1's son, these scars appearing after carbuncles on the nape of the neck. This man also recovered extremely slowly from ordinary cuts. A cousin stated that she always recalled the "peculiar skin color" of this man, which was compared to that of sib 12-8.

Sib 3-9 had many extensive scars on the knees and elbows, and it is believed that the color of the skin resembled that of sib 3-1 in being "yellow." This man dreaded to shave because of his tender skin.

Members of the family varied in the severity of their manifestations of the syndrome (table 2).

GENETICS OF THE EHLERS-DANLOS SYNDROME

The literature (table 1) contains many references to the inheritance of this interesting syndrome, and by far the majority of authors report a dominant transmission of the anomaly. A perusal of the pedigrees reported by Gilbert,[28] Stuart,[56] and Goldsmith[57] reveals instances of normal persons' transmitting the trait to affected offspring. Lack

56. Stuart, A. M.: Three Cases Exhibiting the Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **30**:984, 1937.

57. Goldsmith, W. N.: Ehlers-Danlos Syndrome, Proc. Roy. Soc. Med. **32**:1027, 1939.

of penetrance of the gene (incomplete dominance) could account for this apparent discrepancy in an otherwise straightforward dominant transmission. It is quite likely, however, that these apparently normal persons actually had the trait but in a very mild form or forme fruste which the examiner failed to recognize. There are, however, many isolated case reports available for study in which it is stated that the parents were normal. Such isolated cases may be interpreted genetically from several angles: 1. The person may represent an autosomal recessive form of the disease, he receiving the abnormal gene from both

TABLE 2.—*Manifestations of the Ehlers-Danlos Syndrome by Members of Kindred 534*

Sib	Papyraceous Scars	Hyperelastic Skin	Hyperextensibility of Joints	Fractures	Subcutaneous Nodules	Obesity	Bronze Color of Skin	Acrocyanosis
6-1	+	+	..	+	..	..	+	..
7-2	+	++	+	..	..	..	+	..
7-4	+	++	++	++	..	+	+	..
7-5	++	++	±	..	+	..	+	+
7-6	++	±	..	..	..	++	..	..
7-8	+++	+++	++	++	..	++	+	++
7-9	+	++	+	+	..	..	..	..
7-12	±	++	..	..	..	..	+	..
12-4	+	+	+	..	..	..	..	..
12-6	++++	++++	++++	+	++++	++	++	++
12-8	++++	++++	++++	±	++++	+	++	+
12-9	..	++	..	..	..	..	++	+
12-10	+	+	..	..	..	..	±	..
14-5	++	++	++	..	..	..	+	..
14-6	+	++	+	..	..	..	..	..
14-7	..	±	..	..	..	..	..	..
14-8	+	++	+++	..	..	..	++	+
14-9	++	++	++	..	..	..	++	..
14-11	+	+	++	..	..	..	+	..
18-2	+	++	±	+	..	..	+	..
20-1	++	++	+	..	..	..	+	+
21-1	++	+	..	++	..	..	..	..
21-3	++	++	+++	..	..	..	+	+
21-4	+	+	..	..	..	..	±	+

parents. In such cases consanguinity of the parents gives strong support to this possibility. 2. The person may represent the expression of a sex-linked gene transmitted by female carriers. This gene could be present in many generations of female carriers before the appearance of an affected male member. 3. The affected person may be the expression of a mutation in the germ plasm of one of his two parents, and it will be necessary to study this person's offspring before the type of inheritance can be ascertained. Schlafenhausen's (1934) report of a family showing hypermobility of the joints of the hand suggests a recessive inheritance of a mild form of the syndrome.

The pedigree of the reported kindred, 534, suggests a definite dominant inheritance pattern of transmission of the anomaly. In the

thoroughly studied sibships there is revealed a higher ratio of affected persons than the expected ratio of 1 : 1 of affected to normal siblings. The laws of chance could explain the apparent discrepancy, but it is also possible that an error in diagnosis could account for the distortion. The Ehlers-Danlos syndrome is not a rare disease, in spite of the rarity of medical reports of it, and a great number of persons possess the gene in a very mild form. Some of these last-mentioned persons, the separation between the normal and the affected state being very narrow, tax the diagnostic acumen of the examiner. This statement held true in kindred 534, as it was often difficult to determine the normal from the abnormal, although the examiners actually laid down strict qualifications for determining affected cases.

Diseases inherited as a dominant are rarely encountered in the homozygous state in human studies, and so one must merely speculate that a person demonstrating the heterozygous state will simulate the homozygous condition. In sibship 12 of kindred 534 the children are the offspring of first cousins, both parents being affected with the syndrome. Two of the children in this sibship presented the disease in the greatest degree of severity exhibited in the entire family. It is entirely possible that these 2 girls represent the homozygous state of the syndrome. This postulation is not improbable, in that the gene could be obtained from both parents and also in that the sarcomatous degeneration in sib 12-8 may represent a semilethal effect of the homozygous state. The high incidence of miscarriages in the sibship also suggests that the double dose of the gene may be lethal or semilethal. To prove that sib 12-6 is homozygous we shall have to await the chance to study her offspring, since we could anticipate that all her children would be affected.

COMMENT

The Ehlers-Danlos syndrome is not a rare disease. Many isolated case reports as well as family pedigrees containing several affected persons would support this belief. Our pedigree covering six generations cites 21 affected men and 11 affected women. The fifteen pedigrees referred to in table 1 show 38 affected men and 35 affected women. These figures and ours would support the statement made by several authors that the condition is more prevalent in men. We agree with Ronchese [1a] that many more cases would be recognized if the orthopedic surgeon, in particular, who often sees the articular manifestations of the syndrome, would pay attention to its other manifestations.

The syndrome has appeared under such titles as Ehlers-Danlos, Danlos, Ehlers-Cohn-Danlos, Meekrin-Ehlers-Danlos, dermatorrhexis and cutis hyperelastica. Frequency in the usage of the title Ehlers-Danlos syndrome would suggest that this is the preferable one.

Except to say that the condition is often familial and always congenital, there being no reported cases of acquired Ehlers-Danlos syndrome, we can draw no conclusions regarding its etiology from our case studies. Like Ronchese,[1] we must call it idiopathic.

SUMMARY

The literature regarding the various manifestations of the Ehlers-Danlos syndrome is reviewed.

Two case studies, with a family pedigree of 123 persons, of whom 21 men and 11 women had the syndrome, are given.

The pedigrees listed by other authors are cited.

The variations in the severity of the manifestations of the syndrome between sibs are pointed out.

Photographs of the clinical manifestations of the condition, as well as of the histologic observations and of the roentgenologic findings, are presented.

The pedigree of the reported kindred suggests a definite dominant inheritance pattern of transmission of the anomaly. In the thoroughly studied sibships there was revealed a higher ratio of affected individuals than the expected ratio of 1:1 of affected to normal siblings.

That there were 2 severely affected daughters in a family (sibship 12, fig. 7) resulting from the mating of mildly affected cousins suggests that these girls could represent the homozygous state of the syndrome.

A plea is made for all physicians, particularly orthopedic surgeons, who often see the articular manifestations of the condition, to note the other characteristics of the syndrome.

Department of Dermatology, State of Wisconsin General Hospital.

Department of Ophthalmology, University Hospital.

ABSTRACT OF DISCUSSION

DR. NORMAN TOBIAS, St. Louis: Drs. Johnson and Falls have made a valuable contribution to the literature on the Ehlers-Danlos syndrome, especially from the standpoint of genetics. The inheritance of the condition, a dominant trait, seems to follow the pattern of von Recklinghausen's disease, another member of the nevoid group of disorders.

Since my knowledge of genetics is limited, I shall limit my remarks to the histology of the disease. As the speakers mentioned, the pathologic changes are not always typical. The amount of elastic tissue may be increased (the usual finding), decreased or normal. The amount of collagen tissue may be normal, decreased or increased. Williams as well as Pautrier found the elastic tissue normal. The question naturally arises: Have we been correct in surmising that the elastic tissue plays the main part in this syndrome? I agree in part with McCleod and Muende (Practical Handbook of Pathology of the Skin, New York, Paul B. Hoeber, Inc., 1940, p. 138), who made the following statement:

"From their name, it would naturally be supposed that the elastic fibres possess to a marked degree the powers of extension and retraction, but recent observations

have shown that their elasticity is not really so great as was formerely supposed, and that when they are moderately stretched they rupture. Their elasticity is less than that of the collagenous fibres which is borne out in the striae of pregnancy, where the elastic fibres have ruptured, but the collagenous fibres though stretched and attenuated, are unbroken. The elastic fibres play only a slight role in giving to the skin its elasticity, and the power of extension of the skin is due largely to the involuntary skin muscles. The chief function of the elastic tissue in the skin seems to be supportive. If the elastic tissue fibres were as retractible as the name implies, it would not be necessary for them to form the wavy folded line which the elastic lamina of an artery presents on cross section."

In some cases both the elastic and the collagenous fibers may be involved in the process, and in others only the collagenous fibers. Benjamin and Weiner (*Am. J. Dis. Child.* **65**:247-257 [Feb.] 1943) described a case without elasticity or articular laxity, but with fragility of the skin. In this case there was dense collagenous tissue and an absence of elastic tissue in some areas, and abundant elastic tissue in others. Alexander Brown (*Glasgow M. J.* **27**:7-12 [Jan.] 1946) also described such a case.

Recent studies of collagen fibers with the electronic microscope have demonstrated that they are quite wavy and cross striated or banded and have great expansibility and tensile strength.

However, one point in favor of the elastic tissue theory is that elastic tissue attracts calcium while collagen tissue does not. This observation may explain the dermal tumors in the syndrome. Of course, necrotic fat also attracts calcium, but many of these spheroid tumors can be visualized by roentgenologic examination before the fat becomes necrotic.

I should like to suggest that future studies include examination of the reticulum or lattice fibers, special staining of the collagen fibers (picrocarmine), a study of the superficial involuntary muscle tissue and the use of dermatoglyphics (Cummings, H.: *Yale J. Biol. & Med.* **18**:551-565 [July] 1946) to demonstrate the trend of faulty development.

Dr. Francesco Ronchese, Providence, R. I.: It is a pleasure to hear a paper so well presented in its clinical, pathologic, roentgenologic and genetic aspects. As far as the frequency of the syndrome is concerned, I believe a complete syndrome is rare. In the last twelve years I have seen only 1 case in Boston and 1 in New York. Parts of the syndrome, as observed in the many cases listed in this paper, must not be so rare, and the orthopedic surgeon and the internist can certainly help the dermatologist in detecting them. One should be careful, however, not to go too far, including components of too slight or seldom occurrence among the incomplete forms.

I believe that the most prominent feature of the syndrome is the fragility of the skin and the blood vessels, which causes splitting and bleeding and handicaps attempts at surgical operation, as well described in this paper. If this point is remembered, one would not identify the india rubber man of the circus with the Ehlers-Danlos syndrome. The man in the circus may have cutis laxa or cutis hyperelastica but not a fragile skin. The owner of a fragile skin is a crippled or seriously handicapped person, unable to perform in the circus.

Because of the confusion between one or two components of the syndrome and the complete condition, I believe the eponym is not as clear as a short descriptive term stressing the main feature, namely, the fragility of the skin and blood vessels. The observations concerning the subcutaneous spherules are very interesting. With their apparent similarity to the calcified phlebolites, perhaps these spherules could be considered the result of traumatic or spontaneous subcutaneous hemorrhages.

DR. F. A. ELLIS, Baltimore: I wish to call attention to a mild form of hyperelasticity which I think occurs in well over 1 per cent of the population. Persons having it can dorsiflex their fingers 90 degrees or more. They tend to have little acne or the less severe types of acne, and they usually have less cutaneous lesions than the average person. In general, they have the so-called "skin you love to touch"; it is soft, smooth and flexible. This condition is an inherited characteristic. My associates and I expect to make a more detailed report on it in the future. I should like to have Dr. Johnson mention whether or not he has noticed this type of elastic skin and whether or not he thought it was a form fruste or a mild form of the Ehlers-Danlos syndrome.

DR. KURT WIENER, Milwaukee: Striae occur in pregnancy and not in ascites, and occur in Cushing's disease (pituitary basophilism), and not in other diseases of the pituitary gland. They occur in severe states of toxemia and in puberty. Apparently the elastic fibers are an indicator to one or several toxic metabolic agents, and the Ehlers-Danlos syndrome should be studied from this viewpoint.

DR. STURE A. JOHNSON, Madison, Wis.: It is possible, Dr. Tobias, that if one had an opportunity to do a complete postmortem examination on a patient with the Ehlers-Danlos syndrome, he could do the study you suggested. Both you and Dr. Ronchese have mentioned the possibility of changes in the elastic tissue in the aorta and elsewhere. I thank Dr. Ronchese for his remarks. He reported the first case in this country and has completely reviewed the literature.

In osteogenesis imperfecta (fragilitas ossium), Dr. Ellis, one may also find hyperextensibility of the joints. The blue scleras and history of repeated fractures should help one to differentiate this condition from the Ehlers-Danlos syndrome. These changes will be looked for in future cases of the Ehlers-Danlos syndrome.

Dr. Wiener's observation regarding the lack of striae in patients with the Ehlers-Danlos syndrome parallels ours. One mother who had thirteen children failed to show striae of any type.

EVALUATION OF BACITRACIN IN LOCAL TREATMENT OF PYOGENIC INFECTIONS

J. LOWRY MILLER, M.D.
MEYER H. SLATKIN, M.D.
AND
BALBINA A. JOHNSON, A.B.
NEW YORK

THE NEED for safe and effective agents suitable for local therapy in pyogenic infections of the skin is obvious to all physicians. The sulfonamide compounds and penicillin have both proved effective for this purpose; but, unfortunately, with them sensitization occurs in 5 and 10 per cent of the cases, respectively. This often precludes subsequent parenteral administration of these agents in more serious illnesses and so is a drawback to their use in the less severe infections. In March 1948, we reported that the antibiotic bacitracin, in an ointment base, had proved an effective agent in our experience.[1] With the ointment used, refrigeration was necessary to maintain effectiveness.

The present report deals with our further study in the laboratory of the stability and release of bacitracin from various ointment bases kept at refrigerator and room temperatures and with clinical trial of the most promising bases kept at room temperatures during use by the patient.

The discovery of bacitracin by one of us (B. J.) was reported in October 1945.[2] It was found to be produced by a gram-positive, sporulating bacillus of the Bacillus subtilis group. These studies showed that bacitracin was neutral, water soluble, nontoxic and relatively

---

The bacitracin used in this study was produced by the Commercial Solvents Corporation.

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

From the Department of Dermatology, Columbia University College of Physicians and Surgeons and the Vanderbilt Clinic, and from the Department of Surgery, Columbia University College of Physicians and Surgeons.

1. Miller, J. L.; Slatkin, M. H., and Johnson, B. A.: Local Use of Bacitracin, J. Invest. Dermat. **10**:179-188 (March) 1948.

2. Johnson, B. A.; Anker, H., and Meleney, F. L.: A New Antibiotic Produced by a Member of the B. Subtilis Group, Science **102**:376-377 (Oct. 12) 1945.

heat stable. Scudi and associates [3] studied the effect of bacitracin in rats, dogs and monkeys and found little evidence of toxicity except in extremely high doses. Meleney and Johnson,[4] in March 1947, reported favorable response in 88 of 100 patients with surgical infections treated locally. They treated 57 patients, with such lesions as furuncles, carbuncles and abscesses, by injecting an aqueous solution of bacitracin directly into the lesion. They treated 32 patients with bacitracin in an ointment base and the remaining 11 patients with both the solution and the ointment.

In general, it may be stated that bacitracin is effective in vitro against gram-positive organisms, both aerobic (streptococci, pneumococci, staphylococci, micrococci and corynebacteria) and anaerobic (clostridia, streptococci and micrococci), and ineffective against gram-negative organisms (bacilli of the coliform, proteus and pyocyaneus groups), with the exception of the gonococcus and the meningococcus, which are susceptible to its action. Fungi, for instance candida and the cryptococci, are resistant. Spirochetes are highly susceptible.

In our previous study we used an ointment base containing 45 parts of carbowax 4000® [5] and 55 parts of propylene glycol. To this base, 480 units of bacitracin per gram was added immediately before use. The ointment thus prepared retained full potency for two months if kept in the refrigerator but lost 50 per cent of its potency in one week if kept at room temperatures. The propylene glycol caused a mild burning sensation following application of the ointment in a significant number of patients.

In hope of overcoming these objections, it was decided to study the stability and release of bacitracin from a number of ointment bases at ice box and at room temperatures. Miss Anna Grosso, pharmacist of the Presbyterian Hospital, suggested the following ointment bases [6] :

Base No.		
1	Carbowax 4000®	
	Propylene glycol.....	aa (by weight)
2	Carbowax 1540®	50 Gm.
	Carbowax 200®	50 Gm.
	Carbowax 4000®	25 Gm.

3. Scudi, J. V.; Coret, I. A., and Antopol, W.: Some Pharmacological Characteristics of Bacitracin: III. Chronic Toxicity Studies of Commercial Bacitracin in the Dog and Monkey, Proc. Soc. Exper. Biol. & Med. **66**:558-561 (Dec.) 1947.

4. Meleney, F. L., and Johnson, B.: Bacitracin Therapy: The First Hundred Cases of Surgical Infections Treated Locally with the Antibiotic, J. A. M. A. **133**:675-680 (March 8) 1947.

5. Carbowax® compounds are polyethylene glycols of high molecular weight.

6. Lanette wax® is an approximately 10 per cent sulfated or phosphated mixture of cetyl and stearyl alcohols. Hydrosorb® is composed of fatty acid esters of diethanolamine with petrolatum U. S. P. Aquaphor® is an oxycholesterol-petrolatum ointment base.

3	Carbowax 1500®	50 Gm.
	Alcohol U. S. P.	10 cc.
4	Carbowax 1500®	50 Gm.
	Glycerin	10 cc.
5	Carbowax 1500®	50 Gm.
	Liquid petrolatum	10 cc.
6	Carbowax 1500®	30 Gm.
	Propylene glycol	10 cc.
	Starch U. S. P.	30 Gm.
	Zinc oxide	30 Gm.
7	Lanette wax®	20 Gm.
	Glycerin	20 Gm.
	Alcohol U. S. P.	10 cc.
8	Cetyl alcohol	10 Gm.
	Glycerin	10 Gm.
	Sodium lauryl sulfate	1 Gm.
	Distilled water	74 cc.
9	Cetyl alcohol	15 Gm.
	Propylene glycol	10 cc.
	Sodium lauryl sulfate	2 Gm.
	Phosphate buffer, p_H 6.5 q.s.	100 Gm.
10	Lanette wax®	20 Gm.
	White petrolatum U. S. P.	20 Gm.
	Liquid petrolatum U. S. P.	30 cc.
	Distilled water	30 cc.
11	Stearic acid	15 Gm.
	Sodium carbonate	2 Gm.
	Glycerin	15 cc.
	Distilled water	65 cc.
	Alcohol U. S. P.	3 cc.
12	Hydrosorb	
13	Aquaphor®	
14	Petrolatum U. S. P.	

Hereafter the bases described in the tabulation will be referred to by number only.

LABORATORY STUDIES

In this series of experiments, the fourteen ointment bases listed were evaluated as vehicles for bacitracin. A solution of sodium chloride with lyophilized sterile bacitracin (15,000 units per cubic centimeter) was incorporated into weighed samples of the bases to give a concentration of 500 units per gram. The bacitracin solution was thoroughly and evenly distributed throughout the base. The resulting ointments were allowed to stand in the laboratory at room temperature during the test period.

Release of the antibiotic from the several bases was determined by tests made immediately after the bacitracin had been incorporated into the base. In order to test the effect of temperature and/or the

specific base on the stability of the bacitracin, these tests were repeated at intervals for nine weeks.

The release of the antibiotic from the ointments was tested as follows: Five grams of an ointment was weighed out and suspended in 50 cc. of an isotonic solution of sodium chloride in an Erlenmeyer flask. The flask was shaken for from two to three minutes and then incubated at 37.5 C. to allow the diffusion of the antibiotic at body temperature to be tested. Samples of the suspending fluid were withdrawn after four and twenty-four hours. These samples were then

TABLE 1.—*Recovery of Bacitracin from Various Ointment Bases After Storage at Room Temperatures**

Ointment No.	Ointment Base †	Percentage of Bacitracin Released into a Surrounding Isotonic Solution of Sodium Chloride During a Diffusion Period of Twenty-four Hours: Age of Ointment (Weeks) 0	1	2	3	4	5	6	9
1	"Carbowax 4000"; propylene glycol	90	50	42	..	32	..	10	..
2	"Carbowax 1540"; "Carbowax 200"; "Carbowax 4000"	85	60	50	..	26	..	15	..
3	"Carbowax 1500"; alcohol U. S. P.	80	45	35	..	18	..	6	..
4	"Carbowax 1500"; glycerin	67	52	38	..	15	..	11	..
5	"Carbowax 1500"; liquid petrolatum U. S. P.	75	43	25	..	7.5	..	5	..
6	"Carbowax 1500"; propylene glycol; starch U. S. P.; zinc oxide	88	40	..	35	..	30	..	..
7	"Lanette wax"	45	40	28	..	16	..	1.5	..
8	Cetyl alcohol	90	95	95	..	52	..	54	32
9	Cetyl alcohol	95	80	..	38	..	42	..	..
10	"Lanette wax"	72	72	68	..	24	..	24	13
11	Vanishing cream	52	7.6	..	4	..	..	..	..
12	"Hydrosorb"	2.9	4.5	..	0	..	..	..	..
13	"Aquaphor"	4	0.5	..	0	..	..	..	..
14	Petrolatum U. S. P.	..	2.4	4.3	..	1.9	..	2.1	3.8

* The ointment contains 500 units per gram.
† The exact composition of the numbered ointment bases is given in formulas in the text.

diluted with distilled water (1:20), and the concentration of bacitracin was determined by the agar plate–penicylinder assay method, using the Commercial Solvents Corporation strain of Micrococcus flavus as the test organism. When the results of tests showed that only a small percentage of the antibiotic was released, the undiluted suspending fluids were assayed directly. The results of tests made with the fourteen ointments are given in table 1. Since these results represent bioassays, they are subject to the ± 5 to 10 per cent error inherent in all such assays.

The percentage of recovery obtained when the ointments were tested immediately after the bacitracin was incorporated represents the release of the antibiotic from the base. A drop in the percentage

of recovery in tests made after one to nine weeks' storage must be interpreted as lack of stability of the antibiotic in the base.

As shown in table 1, certain bases, such as petrolatum and aquaphor,® released minimal amounts of the antibiotic when suspended in saline solution. Additional tests were run, using distilled water, phosphate buffer solution, p_H 6.5, and citrated human plasma as the suspending fluids, with saline solution as the control. The release into all the fluids was approximately the same.

We also tested the release from the grease bases by spreading a thin layer of the ointment on fine mesh gauze and then suspending the gauze in an isotonic solution of sodium chloride or citrated human plasma in a large Petri dish. This difference in the technic of the tests did not result in an appreciable increase in the percentage of the antibiotic released when compared with the results of the flask test.

Since it was regularly found throughout the entire storage period that the recovery of bacitracin from the petrolatum base was only 2 to 4 per cent, it became desirable to know whether this was due to poor release or to destruction of the antibiotic. A sample of this ointment that had stood at room temperature for two months was subjected to a further test. Two 5 Gm. samples of the ointment were weighed out. One was suspended in 50 cc. of isotonic solution of sodium chloride and the other in phosphate buffer solution, p_H 6.5. These suspensions were then heated until the ointment had completely liquefied—that is, to 80 C.—and the suspensions allowed to cool to room temperature. The suspending fluids were tested for the concentration of bacitracin. The release was 64 per cent from the sample suspended in saline solution and 56 per cent from the sample suspended in buffer solution. Unheated controls in saline solution released 0.5 per cent of the antibiotic after four hours at 37.5 C. and 3.8 per cent after twenty-four hours. Unheated controls in buffer solution released 0.5 per cent during the four hour period of diffusion and 4.1 per cent during the twenty-four hour period. These results indicate that for the petrolatum base the slow diffusion of the drug is due to poor release from the menstruum rather than to lack of stability of the bacitracin. Solutions of bacitracin in saline or phosphate buffer solution, p_H 6.5, heated to 100 C. for two to three minutes showed no appreciable loss of antibiotic activity.

The percentages of the recovery of bacitracin from the various ointment bases given in table 1 are calculated on the basis of the bacitracin activity of the suspending fluids after a twenty-four hour period of diffusion. Results of tests made after a diffusion period of four hours show approximately the same percentages of release as are seen after the twenty-four hour period for the carbowax® and cetyl alcohol

ointments. The aquaphor,® hydrosorb® and petrolatum ointments showed a release of 0.5 per cent of the incorporated antibiotic during the four hour period, and this increased to 2 to 4 per cent by the end of twenty-four hours. Lanette wax® ointments also showed a gradual, but in this case an adequate, release during the twenty-four period. For instance, after a two week period of storage at room temperature, lanette wax® ointment released 42.5 per cent of the available bacitracin within four hours and an additional 26 per cent during the next twenty hours. It would seem, therefore, that the lanette wax® ointment might act as a more reliable reservoir of the antibiotic when applied to infections. The rapid release of bacitracin from the carbowax® and cetyl alcohol bases has raised the question of maintenance in these vehicles of therapeutic concentrations during the entire twenty-four hour period when such ointments are applied once a day. However, we have tested washings from gauze dressings removed from wounds twenty-four hours after bacitracin in a carbowax 4000® and propylene glycol base had been applied and have found concentrations of bacitracin present in the washings sufficient to inhibit the growth of Staphylococcus aureus.

TABLE 2.—*Results in Treatment of Primary Superficial Infections of the Skin with Bacitracin Ointment*

Diagnosis	Total No. of Cases	Cases Adequately Followed	Cures	Failures	Reaction to Medication	Time Required for Cure: Maximum	Time Required for Cure: Minimum	Time Required for Cure: Median
Impetigo contagiosa	24	18	18	0	0	14	5	8
Folliculitis (beard)	23	16	5	11	0	21	14	16
Infectious eczematoid dermatitis	13	11	10	1	0	30	3	10
Vesiculopustular eruption of hands	10	7	4	3	0	20	10	14
Ecthyma	5	5	5	0	0	32	11	14
Folliculitis (elsewhere than beard)	4	4	3	1	0	14	10	12
Perifolliculitis capitis abscedens et suffodiens	4	2	0	2	0	..	..	..
Dermatitis repens	3	2	2	0	0	21	19	20
Acne varioliformis	3	1	1	0	0	..	..	14
Cellulitis (umbilicus)	1	1	1	0	0	..	..	14
Ulcer (vulva)	1	1	1	0	0	..	..	21
Total	91	68	50	18	0			

CLINICAL STUDIES

Formulas 2, 8 and 10 eliminated propylene glycol and proved best in physical properties and in the stability and release of their bacitracin content. These three were therefore tested clinically. After the addition of the bacitracin, the ointments were kept in the ice box until given to the patient. With ointments 8 and 10, instructions were to keep them at room temperatures, while ointment 2 was to be kept

in the ice box. Five hundred units of bacitracin per gram was incorporated in some ointments and 1,000 units in others.

The majority of our patients were seen in the outpatient clinic. Cultures were taken in all cases to determine the causative organism and to test its sensitivity to bacitracin. Crusts had to be removed in superficial pyodermas to permit contact of the ointment with the active process. This we accomplished by means of hot compresses soaked with isotonic solution of sodium chloride, in order to avoid

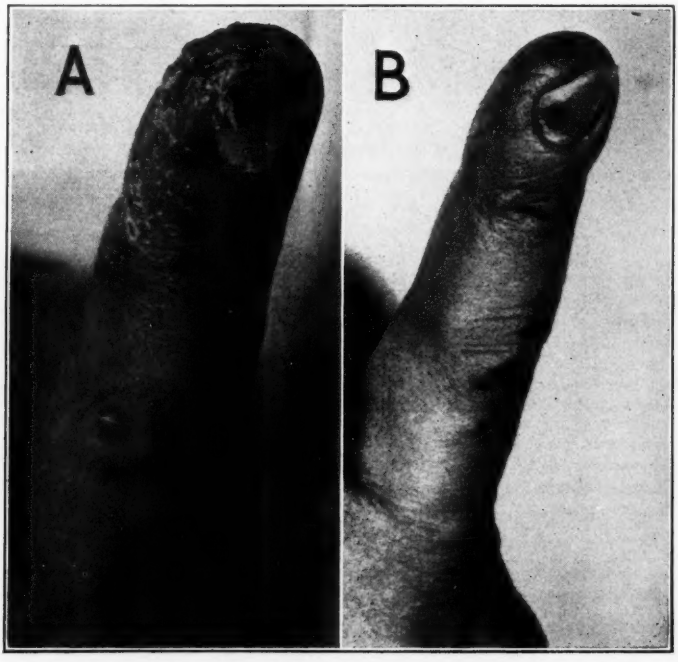


Fig. 1.—*A*, dermatitis repens, of eighteen months' duration; *B*, clearing after twenty-one days' treatment with bacitracin ointment.

the irritation frequently seen when soap and water are used for this purpose. Oxidizing agents, such as hydrogen peroxide and potassium permanganate, inactivate bacitracin and should not be used. The ointment was applied twice a day, according to this procedure.

RESULTS

Results of treatment of 68 patients with primary superficial infections with bacitracin ointment are shown in table 2. For 18 patients with impetigo, followed for at least two weeks after supposed cure and after

stopping of all treatment, the median time of cure was eight days. This is the same figure as was found in our previous studies of bacitracin.

Clinical and bacteriologic differentiation between simple folliculitis and sycosis vulgaris is almost impossible except on the basis of duration

Fig. 2.—*A*, vesiculopustular eruption of the hands, of six weeks' duration; *B*, appearance after eight days' treatment with bacitracin ointment.

of infection. In this series of 16 patients, 5 are listed as being cured; of these, 3 had had their infection for only two or three weeks. The remaining 2 patients listed as being cured had had their infection for

one year and one and one-half years, respectively. One has been followed for one hundred and five days and is still well. Of the 11 patients for whom the treatment is listed as a failure, 6, in reality, have the infection controlled by bacitracin ointment. They are free of lesions as long as they use the ointment. They have been followed from forty-five to one hundred and eighty days, and in no case have we seen evidence of sensitization of the skin. The treatment failed to cure 5 patients.

Under the heading of vesiculopustular eruptions of the hands are listed patients for all of whom repeated cultures for fungi had been sterile. Of the 3 patients for whom treatment is listed as having failed, 2 showed definite improvement.

TABLE 3.—*Results in Treatment of Secondary Infections in Various Dermatoses*

Dermatoses with Secondary Infection	No. of Cases			Reaction to Medication		Time Required for Cure		
	Total No. of Cases	Adequately Followed	Cures	Failures		Maximum	Minimum	Median
Dermatophytosis	8	6	6	0	0	18	4	12
Allergic eczema	6	6	6	0	0	21	9	12
Varicose ulcer	4	4	4	0	0	..	..	..
Neurodermatitis	2	2	2	0	0	21	14	18
Scabies	2	2	2	0	0	14	7	10
Seborrheic dermatitis	1	1	1	0	0	..	..	14
Contact dermatitis	1	1	1	0	0	..	..	12
Acrodermatitis atrophicans chronica	1	1	1	0	0	..	..	16
Total	25	23	23	0	0			

The 2 patients with dermatitis repens had had the disease for one and one-half and for three years, respectively. Many forms of treatment, including use of the sulfonamide compounds and penicillin, had been tried without success. The eruption cleared in an average of twenty days. The patients have been observed for two and for five months and have remained clear of lesions, without treatment.

No beneficial effect from bacitracin ointment was obtained in cases of seborrheic or contact dermatitis or of cystic acne.

In the group of patients with dermatoses with secondary infections listed in table 3, bacitracin ointment cured the secondary infection but proved of no value against the primary dermatosis. The time of cure of the secondary infection complicating varicose ulcer is left blank, as recurrence of infection is the rule and requires retreatment.

Lack of space prevents us from reporting in tabular form the bacteriologic findings, which were determined in all cases. In general, they corresponded with those reported in our previous paper. The

studies for sensitivity of the organisms to bacitracin also are not listed, for the same reason. These studies confirm the general statement made

TABLE 4.—*Median Time of Cure with Nonrefrigerated Bases and Refrigerated Carbowax® Base Containing Bacitracin*

Disease	Ointments 8 and 10, Nonrefrigerated		Ointment 2, Refrigerated	
	Number of Cases	Median Time of Cure	Number of Cases	Median Time of Cure
Impetigo contagiosa	10	7.5	8	9
Infectious eczematoid dermatitis	5	6.0	5	14
Vesiculopustular eruption of hands	2	12.0	2	17
Ecthyma	3	11.0	2	23
Folliculitis elsewhere	2	11.0	1	14
Dermatitis repens	1	21.0	1	19
Secondary infection in				
Allergic eczema	4	10.5	2	19
Dermatophytosis	4	8.0	2	15

TABLE 5.—*Results in Treatment of Superficial Infections of the Skin with Various Chemotherapeutic Agents*

Disease	Ointment Used	Number of Cases Adequately Followed	Cures	Failures	Reaction to Medication	Median Time of Cure
Impetigo contagiosa	Bacitracin	44	42	2	0	8
	Penicillin	91	89	2	2	5.8
	Sulfonamide drug	45	44	1	1	6
	Nitrofurazone ("furacin")	16	15	1	0	8
Folliculitis (beard)	Bacitracin	32	14	18	0	19.5
	Penicillin	15	8	7	2	11
	Sulfonamide drug	12	5	7	1	45
	Nitrofurazone	4	3	1	1	12
Ecthyma	Bacitracin	18	18	0	0	14
	Penicillin	14	13	1	1	8
	Sulfonamide drug	12	12	0	0	18
	Nitrofurazone	2	1	1	0	11
Infectious eczematoid dermatitis	Bacitracin	21	20	1	0	9
	Penicillin	1	1	0	0	5
	Sulfonamide drug	..	..	..	..	..
	Nitrofurazone	..	..	..	..	..
Folliculitis (elsewhere than beard)	Bacitracin	12	10	2	0	17
	Penicillin	14	13	1	0	10
	Sulfonamide drug	2	1	1	0	42
	Nitrofurazone	4	4	0	0	10
Secondary infection in						
Allergic eczema	Bacitracin	12	12	0	0	11
	Penicillin	4	4	0	0	7
	Sulfonamide drug	5	5	0	0	14
	Nitrofurazone	2	2	0	0	11
Contact dermatitis	Bacitracin	5	5	0	0	11
	Penicillin	2	1	1	0	..
	Sulfonamide drug	..	..	..	..	..
	Nitrofurazone	4	4	0	0	19

previously in this paper concerning sensitivity and resistance of different organisms to bacitracin. Evidence for development of bacitracin-resistant strains was also gathered. A twofold to eightfold increase in

resistance was found in a few instances, but this had no apparent influence on clinical results.

In the laboratory tests 68 per cent of bacitracin could be recovered from ointment 10 after storage at room temperatures for two weeks, and 95 per cent from ointment 8 under the same conditions. The ready release and adequate stability of bacitracin in these ointments seemed to justify clinical trial for periods of up to two weeks without refrigeration. In table 4 are found the results in cases in which ointment 8 or 10 was used and kept at room temperatures during the period of treatment and the results in cases in which ointment 2 was used and kept in the ice box during the treatment period. Carbowax® ointment 2 was chosen as a control, since the laboratory test showed 85 per cent recovery of bacitracin after two weeks if the ointment was kept under refrigeration. No better clinical results were obtained with ointments containing 1,000 units of bacitracin per gram than with those incorporating 500 units.

In our previously reported series, patch tests performed in 74 cases to elicit sensitivity to bacitracin subsequent to treatment gave consistently negative results. In the series now under discussion, this procedure was therefore not repeated.

Table 5 summarizes for comparative purposes our experiences with bacitracin and those previously reported with penicillin,[7] the sulfonamide drugs[8] and nitrofurazone (furacin®)[7] in ointments for the treatment of pyogenic infections of the skin. In this table the present series and the series previously reported are combined.

COMMENT

An analysis of table 1 shows that the release of bacitracin follows the same pattern as the release of other water-soluble chemotherapeutic agents from grease, oil in water, and greaseless bases; that is, only a small fraction of the incorporated antibiotic is released by the grease bases, whereas practically all is made available when a water-miscible base is used. This observation is in agreement with the findings of Pillsbury and associates,[9] who showed clinically that sulfathiazole was not so effective in an all-grease base as in an oil in water emulsion base.

7. Miller, J. L.; Rodriguez, J. J., and Domonkos, A. N.: Evaluation of Penicillin in Topical Therapy, New York State J. Med. **47**:2316-2321 (Nov. 1) 1947.

8. Miller, J. L.: Use of Sulfanilamide and Its Derivatives in Ointment Form: Local Treatment of Cutaneous Diseases, Arch. Dermat. & Syph. **46**:379-385 (Sept.) 1942.

9. Pillsbury, D. M.; Wammock, V. S.; Livingood, C. S., and Nichols, A. C.: The Local Treatment of Pyogenic Cutaneous Infections with Sulfathiazole in an Emulsion Base, Am. J. M. Sc. **202**:808-822 (Dec.) 1941.

Bandelin and Kemp [10] demonstrated in the laboratory that the release of sulfonamide compounds from oil in water bases was superior to that from grease bases. Zheutlin and Fox,[11] in a series of laboratory experiments, found that grease bases, water-absorbing and water in oil emulsions release little sulfadiazine sodium, whereas oil in water and water-miscible bases release much larger amounts of the same drug.

As a result of our findings in the laboratory and after analysis of the results of clinical trial, as shown in table 4, we believe that bacitracin ointments 8 or 10 can be kept for a limited time at room temperature without losing therapeutic effectiveness. Thus, with these ointments there is no need for refrigeration if they are to be used over a short period. We feel that 500 units per gram is sufficient to cover the anticipated 40 to 50 per cent deterioration of antibiotic activity.

Analysis of tables 2 and 3 confirms the impression gained from our previous work that bacitracin is an effective agent for local therapy of pyogenic infections of the skin. In table 5, the effectiveness of bacitracin is shown to approximate that of penicillin, the sulfonamide drugs and nitrofurazone. The real superiority of bacitracin rests in the low rate of sensitization of the patient, 0.5 per cent, as so far found. All the results summarized in table 5 were obtained before the respective agents had come into general use, which situation holds for bacitracin at the time of writing. However, in its early use, penicillin sensitized 6 per cent of patients, the sulfonamides, 5 per cent, and nitrofurazone, 5 per cent. Prolonged use of any medication is more frequently followed by sensitization. We have used bacitracin for as long as three hundred days in the same patient without producing reaction. In cases of infectious eczematoid dermatitis and folliculitis of the beard a contact dermatitis–like reaction from medication is likely to occur. We have encountered no such reaction with bacitracin. In fact, we used bacitracin ointment successfully in treatment of a patient with folliculitis of the beard who at the time had a dermatitis from use of sulfathiazole ointment.

CONCLUSIONS

Bacitracin ointment, in a concentration 500 units per gram, is an effective agent against superficial pyogenic infections of the skin.

Oil in water, and greaseless carbowax® bases have been found best for stability and release of bacitracin in laboratory tests.

Formulas are given for two ointment bases in which bacitracin remains therapeutically effective for at least two weeks without refrigeration.

---

10. Bandelin, F. J., and Kemp, C. R.: The Evaluation of Various Bases for Sulfonamide Ointments, J. Am. Pharm. A. **35**:65-71 (March) 1946.

11. Zheutlin, H. E. C., and Fox, C. L., Jr.: Use of Diffusion Rates in Evaluating Ointment Vehicles for Antibacterial Therapy, to be published.

The low rate of sensitization of the patient, 0.5 per cent, is emphasized. Prolonged use has not increased the percentage of reaction.

The effectiveness, coupled with the low sensitizing potential, of bacitracin suggests its use particularly in such diseases as infectious eczematoid dermatitis, in which reactions are prone to occur.

Bacitracin is compared with penicillin, the sulfonamide drugs and nitrofurazone for effectiveness and percentage of reaction.

371 Park Avenue.

ABSTRACT OF DISCUSSION

DR. JAMES R. DRIVER, Cleveland: The ultimate importance of bacitracin will depend on its success where penicillin and the sulfonamide drugs have failed.

The necessity for refrigeration is at present a disadvantage, but Dr. Miller and his associates have at least partially overcome this problem by increasing the bacitracin content of their preparations beyond that necessary for therapeutic efficiency.

When asked to discuss this paper, about three months ago, I had had no clinical experience with this agent. From the Ben Venue Laboratories in Bedford, Ohio, I was able to secure a limited amount and have used it over a short period of eight weeks in 23 cases of pyogenic infections of the skin, of varying types.

The ointment base used was that suggested by Meleney and Johnson in their paper published in March 1947. It was made of 45 parts carbowax 4000® and 55 parts propylene glycol. The strength of bacitracin was 100 units per gram. A later bioassay of the ointment revealed, however, that it contained only 82 units per gram. This concentration, of course, is less potent than the strength of 400 to 500 units per gram used by Dr. Miller and his co-workers.

All my patients were treated by applications of the bacitracin ointment twice daily. The affected parts were cleansed with soap and water or by boric acid solution before each application. I realize that the results would probably have been better had the bacitracin strength of the ointment been greater. There were 5 patients with impetigo, all cured in less than ten days. One patient with folliculitis keloidalis was appreciably improved after two weeks. A patient with a severe case of infectious dermatitis of the legs, with bilateral lymphangitis and a high fever, was hospitalized. Bacitracin ointment was used along with intramuscular injections of penicillin every three hours. There was a remarkable recovery in ten days.

In general, the results of the treatment of secondary infections in various dermatoses were not particularly encouraging, and, after varying lengths of time, from one to four weeks, other forms of therapy were substituted. In the group of patients with secondary infections there were instances of early improvement which failed to continue or those in which the eruption became worse. In other instances there was an unsatisfactory result.

In the group with unsatisfactory results there were 4 patients with infectious dermatitis superimposed on contact dermatitis, 2 patients with varicose ulcer with surrounding infectious dermatitis and 2 patients with infected atopic eczema. In another patient with infectious dermatitis of the face, remarkable improvement occurred in the first week, but an exacerbation after the second week was suggestive of a possible sensitization. One patient with dermatitis repens was practically cured after four weeks, but a severe exacerbation developed on continuance

of the treatment. There was no improvement in 2 patients with nummular eczema, 1 with sycosis vulgaris and 1 with ulcus vulvae acutum.

It is not fair to compare these results with those of Dr. Miller and his associates, inasmuch as the strength of the bacitracin in the preparations used was not comparable, and the presence of propylene glycol may have caused some irritation. In my opinion, however, it will be only after an extensive experience by many investigators that the ultimate evaluation of this promising new antibiotic will be made.

DR. WILLIAM R. LOVE, Dayton, Ohio: Dr Miller and his co-workers have accomplished a very efficient evaluation of bacitracin as applied topically in the treatment of pyogenic bacterial cutaneous infections. This has been done through the use of sound, nonvariable fundamental investigative principles. Dr. Miller is specially qualified because of his previous experience in the study of sulfanilamide and its derivatives when used in an ointment vehicle and because of his experience in the evaluation of penicillin topically applied.

Some factors which must be considered in the preparation of a suitable bacitracin ointment are stability, dispersion of the bacitracin in the proper medium, diffusion from the base, concentration and sensitization. Bacitracin ointment is of value in treatment of those superficial infections which are caused by microorganisms which are inhibited by bacitracin, of penicillin-fast infections and of streptomycin-fast infections. In cases of deep infections, infections of unknown cause, infections with organisms resistant to bacitracin and cutaneous conditions in which the use of greases is contraindicated, for example, bacitracin ointment mixtures should not be used. Eczematous contact reactions and other forms of hypersensitivity of the skin and mucous membranes are seldom seen after topical bacitracin therapy.

Early pharmacologic studies show bacitracin to be nephrotoxic. An increase in albuminuria, along with an increased number of urinary casts found, has occurred in human subjects within three days when bacitracin is given parenterally in intramuscular doses of 12,000 units every six hours. It is essential that the blood urea nitrogen be determined every two or three days and advisable that administration of the drug cease with any pronounced increase of the blood urea nitrogen, in order to prevent damage to the kidney. With the nephrotoxicity in mind I should be inclined to advise against a covering of large denuded body surfaces with bacitracin in solution or in ointment form. In some cases of extensive infectious eczematoid dermatitis, excoriation and denudation could readily be sufficient to allow absorption of bacitracin to a degree which might be hazardous to the patient.

Shelf testing of an antibiotic vehicle determined by the diffusion method described in Dr. Miller's study is the most reliable available procedure, even though it might carry a ± 5 to 10 per cent error. Buffers have been shown not to be of great value in increasing the therapeutic efficiency of penicillin. As presented today the use of buffers is probably of little value in bacitracin therapy.

Lanette wax® used as the vehicle provided a reliable reservoir, with adequate release of bacitracin; petrolatum is likewise a good vehicle. Both are limited and sometimes contraindicated in their application on certain areas of the body and in some conditions of the skin because of their greasiness. Oil in water emulsion colloid bases are more generally applicable to all body areas and may proved to be the most adaptable vehicles for bacitracin.

Bacitracin is comparable to penicillin in the mode of administration and in the types of gram-positive bacteria which it inhibits. Bacitracin maintains a therapeutic blood concentration longer than does penicillin.

Dr. J. Lowry Miller, New York: Dr. Driver's results more or less confirm what we found, namely that when we used 100 units per gram our results were relatively unsatisfactory. I am glad that he obtained as good results as he did in some of the cases.

Dr. Love wisely emphasized the toxic possibilities when bacitracin is used internally. We did not wish to say that bacitracin was necessarily nontoxic. We feel that, beyond question, it is nontoxic when applied locally. We have used it over extensive areas and have done repeated determinations of blood levels. We feel that there is no danger of toxicity from the small amounts absorbed. Considerable work is being done on the internal use of bacitracin, which fact gives promise that the toxic features may be eliminated.

The main point that we wished to emphasize was that, so far, at least, the drug had caused sensitization in a very low percentage of cases.

Society Transactions

PHILADELPHIA DERMATOLOGICAL SOCIETY

Carmen C. Thomas, M.D., *Chairman*

Reuben Friedman, M.D., *Secretary*

March 16, 1945

Pyogen Allergic Dermatitis. Presented by Dr. John W. Lentz.

E. C., a white man aged 53, presents an erythematous, vesicopapular and pustular dermatitis of the face, tending to be follicular. There is also diffuse swelling of the upper lip, with keratitis and conjunctivitis of the left eye. In 1940 there was swelling of the right side of the face with erythema and pustulation. After several months the right eye became involved, and eventually there resulted panophthalmitis necessitating enucleation. Several months ago there was a flare-up of the dermatitis of the face with involvement of the left eye, in which conjunctivitis and keratitis developed. This involvement improved with therapy, but a cure of the condition has not, so far, been obtained.

A culture of the pustules produced a hemolytic Staphylococcus-Streptococcus infection. Repeatedly performed blood cell counts, serologic tests of the blood for syphilis, urinalyses and glucose tolerance tests yielded no abnormal results. No foci of infection were found except for clouding of the right maxillary antrum and ethmoidal cells demonstrable in a roentgenogram.

Treatment has consisted of compresses with a solution of potassium permanganate and the local application of sulfathiazole. Improvement was mild. Decided improvement occurred with the "desensitization" use of Staphylococcus ambotoxoid. The most striking result was obtained with sodium penicillin, administered every three hours for eight days, with a total of 1,200,000 units given intramuscularly. Roentgen rays were not administered because of the history of previous roentgen therapy of unknown amount.

DISCUSSION

Dr. Claus Jordan, Stroudsburg, Pa. (by invitation): It looks like a case of elephantiasis nostras of the face.

from edema which is simply reactive against absorbed toxins of bacteria. Why is the allergic mechanism necessarily invoked instead of a simple toxic mechanism?

Dr. Fred D. Weidman: I should like to ask how this is to be distinguished

Dr. John W. Lentz: This patient is seriously ill. He has lost one eye already and has suffered temporary blindness during the second episode. Everybody who saw him has agreed that penicillin has at least temporarily saved the remaining eye. I do not know whether more penicillin should be administered locally and intramuscularly in smaller doses over a longer period of time. I await therapeutic suggestions.

Dr. Carroll S. Wright: There is one preparation, alibour water, which I have seen affect favorably some inflammatory conditions of this type. Its use certainly can do no harm.

DR. HERMAN BEERMAN: What is the diagnosis? This is a pyogenic dermatitis; but what does that mean? It is not pyoderma in the ordinary sense. What is it?

DR. FRED D. WEIDMAN: I asked that question because penicillin is now in the picture and there is a history that the condition improved with its use, suggesting that the dermatitis is the result of bacterial activity, with toxic products. The mechanism is a toxic and not necessarily an allergic one. The factor of penicillin in this presentation introduces as a topic for discussion the question whether many conditions so called are in fact allergic in their mechanism or simply toxic.

DR. JOHN W. LENZ: I have had 2 patients, each of whom had a focus of infection and osteomyelitis and, in addition, nummular-eczema-like plaques disseminated on the body. In 1 case the condition completely cleared, and the osteomyelitis subsided with the use of roentgen rays and penicillin. The disease in that case was regarded as a so-called bacterid. I wonder now whether that was really bacterial dermatitis. The other patient responded fairly well to the use of penicillin but later relapsed. After the use of additional penicillin, he made a complete recovery.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: Injections of foreign protein in the form of milk might help this man.

DR. CARMEN C. THOMAS: Treatment with hydrochloric acid might also help.

Pustular Psorias. Presented by DR. EDWARD F. CORSON.

A. C., a white man aged 35, robust and health looking, presents on both palms rather sharply bordered inflammatory patches involving from one third to one half the areas of those regions. These patches are formed of thickly studded pustules and crusts on a red slightly swollen base. The nails of the fifth fingers are partly separated from their beds, apparently lifted by crusts which also surround the nail folds. There are rounded scaly areas on the soles or near by and at and below the elbow tips. The patient was an instrument repairer until recently, when he took a clerical position. In October 1944, white "pimples" developed on the left palm. The other palm and the tips of the fifth fingers later became involved, especially around the nails. The other nails are streaked and dystrophic. Results of several examinations of the scales for fungi have been negative.

DISCUSSION

DR. FRED D. WEIDMAN: I agree with the diagnosis. This would be a case most acceptable to the MacKee group, which contends that the condition is psoriasis. The Andrews group contends that it is not. The fact that, as Dr. Corson says, the nails are involved and that lesions occurred on the elbows shows them to be in the right places for psoriasis, which the MacKee group would emphasize in supporting their thesis. I think that the matter is not yet entirely settled. Often in medicine, not alone in dermatology, two diametrically opposed views are reconciled by discovery by the two groups that they are not talking about the same thing and that both parties are right. I think that there is still room for the belief that there may be such as thing as pustular psoriasis and that there may be such an entity as a recalcitrant pustular eruption. This case would fit in with the picture of pustular psoriasis.

Atrophoderma Due to Roentgen Rays. Presented by DR. JOHN W. LENTZ.

Psychogenic Localized Hyperhidrosis. Presented by DR. JOSEPH V. KLAUDER and DR. FRANCIS B. EVELAND.

A. A., a white boy aged 11 years, presents on the lower half of the nose beads of perspiration that disappear and reappear. There is mild redness of this part of the nose, the upper border of which is rather sharply marginated and corresponds to the cartilaginous portion of the nose. The mother stated that when he gets nervous the nose becomes red and beads of perspiration appear. In addition, hiccup developed. At the onset, in the summer of 1944, there was only redness. About one month ago beads of perspiration appeared in addition to the redness. There is no clue in the history as to a circumstance that may have suggested to the patient the onset of the condition. The mother has a moderately red nose and face, as part of rosacea. There are two other boys in the family, one older and one younger than the patient; both are in good health.

Examination disclosed, in addition to the nasal condition, that the right pupil is larger than the left. The ears are somewhat red. The teeth are poorly formed. The palate is highly arched. The patient is poorly nourished and has a scaphoid scapula. There is no sweating of the palms or soles or vasomotor circulatory disturbance except possibly the redness of the ears. The pulse rate is 86.

DISCUSSION

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I think that the patient has granulosis rubra nasi.

DR. FRANCIS B. EVELAND, Wilkes-Barre, Pa.: This patient seemed to present the picture which Dr. Schildkraut mentioned—granulosis rubra nasi. The question has been raised as to whether this is due to a sympathetic cervical nervous disorder.

DR. THOMAS BUTTERWORTH, Reading, Pa.: Is it not true that these conditions clear up spontaneously at puberty?

A Case for Diagnosis (Weber-Christian Disease? Sarcoid? Darier Roussy?). Presented by DR. JOHN W. LENTZ.

A Case for Diagnosis (Lymphogranuloma Venereum of the Face?). Presented by DR. JOHN H. STOKES and DR. MARSHALL GUTHRIE (by invitation).

W. C., a Negro aged 19 years, well developed, in no pain or distress, presents large masses in his right and left cheeks. The one over the ramus of the left mandible gives the sensation of induration and firmness at the center of the mass. No other lesions are present. There is no pain or tenderness. The swelling was first noticed in 1939, starting as a small lump on the left cheek, which gradually increased in size. A year or two later a second lump appeared in front of the right ear. In 1941 several nodes were removed from his neck. Despite all treatment, the lesions have gradually increased in size. A biopsy was performed in 1944, and the diagnosis was "chronic granuloma." The patient stated that the lesions become larger when he is exposed to sudden changes in temperature.

Results of Frei and Ducrey cutaneous tests have been positive repeatedly. The complement fixation tests for lymphogranuloma venereum gave positive reactions. Serologic tests for syphilis have given negative reactions on three different occasions.

The patient has had two courses of sulfathiazole and has been given antimony potassium tartrate by the intravenous route. So far the results have not been striking.

DISCUSSION

DR. FRED D. WEIDMAN: The involvement of the parotid gland, on one side, at least, suggests Mikulicz' disease as a possibility and also the parotitis which occurs in Schaumann's disease. However, both of these diseases can be excluded in the absence of other supporting symptoms. In the histologic sections there were some leukocytes in the centers of the granulomas, and the patient has a positive reaction to the Frei test. The evidence seems to be in favor of lymphogranuloma venereum. Even granuloma inguinale can sometimes occur on the face; I have seen such a lesion on the cheek of a Negro.

Postoperative Gangrene (?). Presented by DR. THOMAS BUTTERWORTH, Reading, Pa.:

S. S., a white nun aged 27, on Oct. 23, 1944, caught her right middle and index fingers in a meat grinder. Two hours later the tips of the fingers were amputated. About a week after the accident blebs developed near the base of the middle finger, and within a few hours gangrene of the skin occurred. Sulfathiazole was employed locally and internally without improvement, and within a few days new gangrenous areas appeared on the adjacent fingers. Penicillin, 15,000 units, was injected morning and night for two days about the base of the fingers. On the second day sloughs appeared at the sites of injection. On Jan. 13, 1945, the patient was hospitalized. Penicillin, 100,000 units daily, and mercurophen® compresses arrested the process, and, on February 14, she was discharged with the second phalanx of the middle finger protruding from a healthy granulating stump. All the other wounds had healed. On February 19, she returned with new gangrenous patches on the second, third and fourth fingers of the right hand. She was readmitted, and, in spite of therapy, new gangrenous areas have appeared in an ascending fashion on the back of the hand and wrist. Treatment has included penicillin given locally and intramuscularly, 30,000 units every three hours. Mercurophen,® (sodium hydroxymercury orthonitrophenolate), tyrothrycin and benzalkonium chloride, 1:2,000, compresses have been used with and without a heat cradle. A blood transfusion and a high vitamin intake were used as supportive measures. The patient now has gangrenous areas, covered by dark brown sloughs and granulating ulcers, on the back of the right hand, wrist and middle finger. Medical and otolaryngologic consultations did not add any significant information.

There was a faint trace of albumin in the urine. The average blood cell count showed 79 per cent hemoglobin, 3,990,000 erythrocytes, 9,050 leukocytes; 16 per cent metamyelocytes (band), 61 per cent neutrophils, 2 per cent eosinophils, 20 per cent lymphocytes and 1 per cent monocytes. Studies of the chemical content of the blood revealed: sugar, 122; chlorides, 477; blood urea nitrogen, 8, and total protein, 6.8 mg. per hundred cubic centimeters of blood. Cultures of the newly involved areas showed, on January 15, Staphylococcus aureus and, on March 7, Staphylococcus albus. Blood cultures were negative.

DISCUSSION

DR. D. M. SIDLICK: I think that it is dermatitis factitia.

DR. HERMAN BEERMAN: I agree.

DR. D. M. SIDLICK: I have seen 2 nuns—both young—who also showed definite clinical evidence of dermatitis factitia. I think that Dr. Butterworth had that diagnosis in mind.

DR. CLAUS JORDAN (by invitation): I suggest immobilization in a cast in true surgical fashion.

DR. THOMAS BUTTERWORTH, Reading, Pa.: That is the diagnosis I wanted to hear. We have searched the patient's room for agents which could produce her lesions. On one occasion I sent her to the department of roentgenology for placebo treatment and, during her absence, went over the room in great detail. The only thing I did not remove that could possibly be used by the patient was a bedside lamp. Some of these gangrenous areas first appear as blebs and then later develop into dark areas. At one time I injected 15,000 units of penicillin around the base of the two fingers that had this gangrenous involvement. I did that the first thing in the morning and late at night. On the second morning she showed much improvement, but on the second night she had a gangrenous area at every point at which I had inserted the needle. That shook my faith in the diagnosis of dermatitis factitia.

Dr. J. M. SCHILDKRAUT, Trenton, N. J.: I suggest that the windowsills outside the room be searched.

DR. CARMEN C. THOMAS: I suggest a trial of amobarbital sodium narcosis. (NOTE.—Dr. Butterworth subsequently reported that on the day following the presentation of this patient at the meeting she was accused of producing the lesions on her hand. She much resented the accusation but within three weeks left the hospital fully recovered.)

A Case for Diagnosis (Tertiary Syphilis or Lupus Vulgaris?). Presented by DR. HERBERT J. SMITH and DR. MEYER L. NIEDELMAN.

Exudative Discoid and Lichenoid Chronic Dermatitis (Sulzberger and Garbe)? Presented by DR. MEYER L. NIEDELMAN.

Donald M. Pillsbury, M.D., *Chairman*

Reuben Friedman, M.D., *Secretary*

March 15, 1946

Acrodermatitis Chronica Atrophicans (Scleroderma?). Presented by DR. ARTHUR G. PRATT.

A Case for Diagnosis (Epidermolysis Bullosa? Bullous Lichen Planus?). Presented by DR. ARTHUR G. PRATT.

A Case for Diagnosis. Seborrheic Dermatitis and Myxedema. Presented by DR. DONALD M. PILLSBURY and (by invitation) DR. JOHN P. SCULLY.

Lupus Erythematosus of the Face with Possible Traumatic or Trophic Causation. Presented by DR. EDWARD F. CORSON.

Pityriasis Lichenoides Chronica (Juliusberg)? Urticaria Pigmentosa? Presented by COMMANDER HAROLD T. ANDERSON (by invitation).

E. S. H., a white man aged 25 years, presents a bilateral symmetric and generalized, tan, discrete, macular eruption. The macules measure about 3 mm. in diameter. The mucosa, palms and soles are clear.

DISCUSSION

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I favor the diagnosis of urticaria pigmentosa. On rubbing the lesions one can bring out distinct urticarial markings.

CAPT. R. L. GILMAN: I think that Dr. Schildkraut's observation is relevant and his diagnosis is clinically logical. When the patient was first seen my colleagues and I were unable to elicit any dermographism. The biopsy specimen was taken in time for this meeting, but, unfortunately, a section was not stained for mast cells, which we shall do later. I am more inclined now to the diagnosis of urticaria pigmentosa.

DR. FRED D. WEIDMAN: This dermatosis impresses me as being telangiectasia. By pressing on these lesions, one can completely extinguish them. I looked for the nevus araneus effect, but could not quite satisfy myself. Fundamentally, this is a punctate eruption. About all that is in favor of urticaria pigmentosa is the fact that dermographia is present, and, after all, one sees that in scabies and pediculosis and other dermatoses.

I did not observe any notable cellular infiltration in the section, and that seems necessary for a tenable diagnosis of urticaria pigmentosa. I cannot attach the name of any dermatologic entity to the condition in this case, but I would recommend that the widespread telangiectatic diseases be reviewed to see what this condition might fit. Tentatively I should be inclined to say that it was widely generalized telangiectasia. One should not here overlook the telangiectasias which are pulsating and which occur on the face and chest, generally in small number, and the significance of which every dermatologist ought to keep in mind, because they are almost invariably associated with cirrhosis of the liver. It was stated that there were some lesions on the face. I did not see any tonight, but I understand that there were some on the face, and attention might be directed to discovering wheher the centers of these are pulsating.

Scleroderma. Presented by COMMANDER HAROLD T. ANDERSON (by invitation).

Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi. Presented by DR. HERBERT J. SMITH and DR. M. H. SAMITZ.

M. K., a Negro aged 85 years, presents on the skin of the shaft of the penis an irregularly patchy, poorly circumscribed, purplish discoloration, also present, but to a less extent, on the prepuce. On the skin on the first metacarpal joint there is a bluish purple, deep-seated discoloration about the size of a quarter but irregular. The lower part of the right leg shows scattered various-sized purplish nodules. There is a patchy purplish hue to the right and left foot and lower part of the left leg, with erythema. The skin of the foot is taut, with definite edema, which does not appear acute. The skin of the right foot appears somewhat verrucous. The condition had its onset about the middle of December 1945, with a sense of burning of the lower part of the right leg and foot. The first time the patient noticed trouble with the foot was after exposure to the sun. This caused burning and "hotness," and he noticed "bumps." The "bumps" have remained.

The reaction of the blood to a serologic test for syphilis was negative on Feb. 15, 1946. A urinalysis and blood sugar determination were also reported as showing no abnormalities. (A biopsy specimen was presented.)

DISCUSSION

DR. FRED D. WEIDMAN: Clinically this condition has much to commend a diagnosis of Kaposi's sarcoma. It is bilateral, except that on the one leg there

are not any nodular elevations, but between the toes there are some definite thickenings and hyperpigmentation. The disease is just more pronounced on one side than on the other. I think that we are all agreed that the general topography of the lesions is consistent with that of Kaposi's sarcoma. I was struck by the avascularity of the lesions; even the most highly projected ones were not red. They were not hemorrhagic; they were pale, as if they contained lymph instead of blood. The regressing lesions are pigmented, but the fully developed ones are not hemorrhagic. In conformity with that, the sections do not show vascular proliferative features. There is lymphangiectasia with a slight intermixture of blood vessels, so that histologically, the picture is not at all that of Kaposi's sarcoma. Kaposi's sarcoma, if nothing else, is a vascular condition. This is the second experience I have had of this sort. In the University Hospital there is another case in which clinically the disease looked like Kaposi's sarcoma but in which there was no vascular intermixture. It makes me wonder whether Kaposi's sarcoma might be going through certain changes. The fact remains, however, that in neither of these cases are there the peculiar hyperplasias without which the diagnosis cannot be Kaposi's sarcoma. It is not typical Kaposi's sarcoma either histologically or clinically. Is it perhaps avitaminosis?

DR. REUBEN FRIEDMAN: The discrepancy between the clinical and histologic features may possibly be due to faulty selection of the specimen for histologic study.

DR. EL MUFTI, Cairo, Egypt (by invitation): I believe that it is a case of Kaposi's sarcoma. I have seen several cases in Egypt in which the disease began on only one leg and after many years extended to the other. I do not believe that there is an avitaminosis factor associated with it.

Tinea Sycosis? Localized Sycosis Vulgaris? Presented by DR. EWARD F. CORSON.

Lichen Urticatus Caused by Dog's Fleas. Presented by DR. LOUIS GOLDSTEIN.

H. B., a white girl aged 12, frail, underweight, overalert, sensitive and of sallow complexion, shows on her neck and upper and lower extremities a papular dermatitis, discrete in its distribution and "shotlike" to the touch. The tops of most of the lesions are excoriated. She has had the usual childhood diseases and, about one year ago, rheumatoid complaints. The present condition began about four months ago as a papular dermatitis which, in the order of its severity, involved the scalp, face, neck and the upper and lower extremities. The lesions, on making their appearance, were paler than the normal skin. They soon turned reddish, and the intense itching that followed caused the child to excoriate her skin to the extent of bleeding, resulting in secondary infection. She was in the habit of holding her dog to her face while playing with him. The animal was infested with fleas during the latter part of last summer, and no chemical means were used to disinfect the animal. Two other children in the same household were unaffected. The urine was reported as being normal. A blood cell count revealed slight hypochromic anemia. A patch test performed with the dog's hair elicited no reaction.

The patient has been given antipruritic lotions, vitamins, iron, parathyroid extract and calcium gluconate and told not to play with her dog. The face and scalp cleared completely, and the rest of her body shows a decided improvement.

DISCUSSION

DR. MORRIS MARKOWITZ: The lesion of a flea bite would be a papule surmounted by a hemorrhagic punctum. There is no such lesion present. Moreover, nobody

else in the family has a similar condition, though the son of the family sleeps with the dog. I think that the more probable diagnosis is scabies. In the webs of the fingers there are papules; the itching is severer at night, and the face is practically free of lesions.

Dr. Bertram Shaffer: I should like to support the diagnosis of flea bites. I think that it is a common enough experience that fleas favor certain persons; they will bite certain persons and not others, much as mosquitoes will. I have seen a girl working at a table with several other girls, and she was covered with flea bites while her companions were not. My impression is that dog fleas do bite human beings. In cases of this sort in which I have eliminated the dog, the patient has recovered.

Dr. A. Strauss: House fleas will live on dogs, but I do not believe that dog fleas will bite human beings.

Dr. Fred D. Weidman: I am not clear as to just what Dr. Goldstein has in mind about papular urticaria being due to flea bites. Does he mean that every one of these lesions is due to a bite or does he mean that there may be some allergic or other mechanism which determines that the eruption takes place according to the mechanism of papular urticaria. I cannot conceive how fleas could pick out precisely the distribution of papular urticaria for purposes of biting.

Dr. Louis Goldstein: Papular urticaria is a common disease, but, strange as it may seem, the dermatologic literature contains relatively little information about it. The book by MacKee and Cipollaro on skin diseases in childhood devotes only one page to it and states that the cause is unknown. Since the information about the subject is so meager, I feel justified in proffering an opinion concerning it. Papular urticaria occurs chiefly in the summer and particularly among poorly nourished children. The disease is less prevalent in less densely populated districts. It is known, too, that food is not a constant factor in that disease and that it may also be caused by insects. I believe that the papules are not directly caused by the insect bites but are allergic manifestations in response to some substance liberated or produced by the insect. This explains the presence of lesions on unexposed parts of the body. Scabies was ruled out in this case because the patient was treated for it without improvement. Furthermore, scabies does not affect the face. When the patient was first seen her face was covered with urticarial papules. It struck me that a contact factor was involved, and questioning disclosed that the child while playing with the dog would hold it to her face. Inasmuch as her skin showed no reaction to a patch test with the animal's hair, the diagnosis of flea bites seemed reasonable. When she accepted my advice to discontinue playing with the dog, the eruption began to clear up. When my advice was disregarded, recurrence of the eruption followed.

Dr. Morris Markowitz: I still cannot imagine the brother sleeping every night with the dog and not getting as much as a bite.

Dr. Louis Goldstein: I think that in papular urticaria there are two factors: one, a predisposing factor, and the other, the allergic factor. In other words, this child is allergic to the dog fleas and the other children are not allergic.

Dr. Henry B. Decker, Camden, N. J.: The children that we see with urticaria are generally plump. Moreover, urticaria does not occur among slum children; ws see it most commonly among healthy children of prosperous families. It occurs in summer because children get a diet with a higher sugar content in summer. I believe that it is a fault of carbohydrate metabolism. All of the children are excessive cracker and chocolate eaters.

DR. BERTRAM SHAFFER: For some time I have had a theory concerning papular urticaria which is identical with that of Dr. Goldstein. I do not believe that it is due necessarily to flea bites, but to any sort of insect bite, including bedbugs and mosquitoes. I think that these children have some sort of allergic response to these insects, as Dr. Goldstein suggests.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I think that there is an allergic factor in scabies. We have all seen cases of apparently cured scabies, but the patients have nevertheless continued to experience itching.

DR. REUBEN FRIEDMAN: I recall an article on papular urticaria in children, published about twelve or fifteen years ago (Corson, E. F.; Perlman, H. H.; Waltz, A. D., and Ash, R.: *J. Pediat.* **48**:349 [June] 1931), in which was reported the results of an exhaustive investigation of 31 cases of this disease. One patient was cured with the clearing up of its oxyuris vermicularis infestation. Another child was found to be sensitive to eggs and milk, and when these foods were eliminated from the diet, the eruption disappeared. No cause was found in any of the other 29 cases. At any rate, the patients showed little or no improvement, regardless of what the laboratory and clinical studies disclosed or of the treatment instituted, dietetic or otherwise.

DR. THOMAS BUTTERWORTH, Reading, Pa.: If the dog fleas had anything to do with it, there would not be so much debate tonight. Outside metropolitan sections there is 1 dog for every 20 persons. In rural sections there is 1 dog for every 3 or 4 persons. If dog fleas were the cause of any dermatosis, that fact would not have been overlooked so long.

A Case for Diagnosis. Presented by DR. BERTRAM SHAFFER and DR. D. M. PILLSBURY.

I. M., a white man aged 38 years, apparently healthy, presents on the plantar aspect and extending up toward the instep an irregular erythematous patch about 6 cm. in diameter. The erythema varies in intensity and has at times a retiform pattern. A slight infiltration can be palpated in certain regions. Six years ago a mass was removed from the patient's pharynx which was histologically reported as schwannoma. Ten months ago he noticed a tender "spot" on the plantar aspect of the left foot. It has gradually enlarged to the present size. The report from a biopsy specimen taken on Oct. 31, 1945, was angiofibroma. Another taken on Feb. 26, 1946, showed only hyperplasia and telangiectasia of blood vessels. The patient has had one roentgen exposure, 50 r through a 0.5 mm. aluminum filter.

DISCUSSION

DR. FRED D. WEIDMAN: Histologically it does not look like a nevus or Kaposi's sarcoma. It looks fundamentally like a fibroma, but vascular in places, and after studying the patient tonight for the first time I surmised that that lesion is of the order of rheumatic nodules. If one presses on one place on the lesion, he flinches; it is a tender spot. There is a wide ramification in the possibilities of tissue changes which can be caused by rheumatism, ranging all the way from granulomatous lesions that look like those of syphilis to those of simple fibrositis. All of us know how much the English have developed the subject of fibrositis. It is only by combining the histologic and clinical features that I am prompted to think in this way, that maybe this condtiion is of the order of fibrositis. The observations of the sections would be compatible with that, and I think that perhaps this is a close an approach to a number of more or less coalescent rheumatic nodules as can occur. Maybe, in the attempt to marshall all these diversified conditions together, a rheu-

matic disease is the most convenient term. I would be inclined to study this patient from the point of view of cardiovascular disease and other circumstances that surround rheumatism.

DR. LOUIS GOLDSTEIN: Phlebitis on the lower extremities is common, but it is unusual to find one on the plantar aspect of the foot. In view of the many varicosities the patient shows in that region, I would not be satisfied with another diagnosis until phlebitis is ruled out.

DR. REUBEN FRIEDMAN: I suggest the possibility that this eruption will in time develop into a typical example of Kaposi's sarcoma.

Nevus Comedonicus. Presented by DR. HERMAN BEERMAN and DR. RALPH H. VAN METER (by invitation).

P. P., a Negro woman aged 21 years, shows lesions in the suprapubic region which have been present since the age of 7 years. The mother described these as large blackheads.

DISCUSSION

DR. HERMAN BEERMAN: I cannot recall, offhand, any cases of the condition in the midline of the body; they are usually unilateral (ARCH. DERMAT. & SYPH. **26**:694 [Oct.] 1937).

DR. FRED D. WEIDMAN: I take it that this is not the first case of this sort that many of us here have seen. The "Corpus Iconum Morborum Cutaneorum" contains many illustrations of conditions with the same distribution as the nevus unius lateris that we already know. That is, there is a somatic factor that determines the distribution in these cases of comedos, just as there is in other forms of nevi, and these comedos are due simply to keratin.

Donald M. Pillsbury, M.D., *Chairman*

Reuben Friedman, M.D., *Secretary*

April 26, 1946

Vascular Nevus. Hemangiomas of the Left Leg and Thigh. Presented by DR. REUBEN FRIEDMAN.

D. S., a white boy aged 15, presents varicosities of the vessels of the outer side of the left leg, with large coalescent patches of purpuric or violaceous bluish discoloration of the anterolateral aspects of the left leg and thigh. Operative scars are present on the outer side and behind the left knee and on the middle of the lateral aspect of the left thigh. The patient was born with bluish red discolorations and tumor-like swellings of the outer side of the left thigh and leg, which grew as he grew older. He had venous ligations performed on Oct. 10 and Dec. 10, 1945, with considerable improvement.

DISCUSSION

DR. DONALD M. PILLSBURY: There is apparently no hypertrophy or bony overgrowth of the affected leg which one sees sometimes with very large extensive nevi of the extremities.

DR. CARROLL S. WRIGHT: Has anybody here had any experience with grenz rays in the treatment of port wine nevi? This patient's lesion is that type of nevus. I understand that good results are now being obtained in the treatment of port wine nevi with grenz rays.

DR. C. S. LIVINGOOD: I recently visited Dr. Bucky and Dr. Koons at Bellevue Hospital and saw a number of their patients being treated with grenz rays and also saw photographs of patients, taken before and after treatment. They believe that it has value. It takes large doses, given over a long period of time. They take patients at any age, but I get the impression that results are not quite as good in older persons. They do not get perfect results in all cases.

Extensive Cavernous Hemangioma Successfully Treated with Solid Carbon Dioxide. Presented by DR. MEYER L. NIEDELMAN.

J. P., a white girl aged 14 months, when first seen presented an extensive cavernous hemangioma extending from the right axilla to the wrist, almost surrounding the entire area. This gradually enlarged until it extended from the axilla to the wrist.

The child has had about twelve applications of solid carbon dioxide, applied for from forty to sixty seconds with moderate pressure about every two weeks. The result obtained was highly satisfactory.

DISCUSSION

DR. MEYER L. NIEDELMAN: Solid carbon dioxide is usually reserved for the treatment of simple or slightly elevated types of angioma, provided that they are on the nonvisible areas of the body. Radium is usually used for the deep cavernous types. This angioma was so extensive that I felt that radium could cause a retardation in bony growth. This case demonstrates that solid carbon dioxide can be used effectively in cases of extensive disease.

Lupus Vulgaris. Presented by DR. CARROLL S. WRIGHT and DR. E. R. GROSS.

Morphea. Presented by DR. REUBEN FRIEDMAN.

R. S., a white girl aged 14, well nourished and well developed, presents an irregular bandlike patch of scleroderma, about 2 to 3 cm. by 7 cm., extending from the vermilion border of the lower lip on the right side to the under surface of the chin. The surface is mottled tan and white; no lanugo hairs are visible, and there is a violet telangiectatic border on the proximal edge.

The patient has been given neostigmine orally and parenterally. Vitamin A and D ointment has been massaged in locally. There has been no improvement; the disease has been spreading slowly.

DISCUSSION

DR. CARROLL S. WRIGHT: I am convinced that bismuth compound works as well in this disease as any other type of therapy. I saw a patient about six weeks ago and again last week. I used oral bismuth sodium triglycollamate and the patient and her physician both were greatly amazed at how much softer the lesion had become in five weeks. In another patient the lesions have almost vanished in a period of two years. She had previously been treated with bismuth compound by injection.

DR. VAUGHN C. GARNER: One must not forget that in morphea the tendency is toward spontaneous improvement and that any therapeutic effort is therefore difficult to evaluate. In localized solitary patches it is justifiable to try roentgen rays in conservative doses. I have been treating a patient with linear morphea of one year's duration who has progressed with treatment given once every three weeks, not exceeding 100 r at each sitting. The use of radon paste has been advocated by

Dr. Pendergrass. It is his contention that it promotes increased vascularization, predominantly of the lymphatic channels. That may not be applicable in this instance, where what is really wanted is blood vascular rather than lymph channel proliferation.

DR. ISADORE ZUGERMAN: I have noted considerable improvement with the use of tetrathione® (sodium tetrathionate monohydrate), a sulfur preparation, in several cases of Raynaud's disease. It has been recommended for the treatment of scleroderma.

Cutaneous Moniliasis (?). Presented by DR. H. H. PERLMAN and DR. L. FRANK.

Atrophic Lichen Planus? Poikiloderma? Presented by DR. LOUIS GOLDSTEIN.

G. R., a white woman aged 55, presents an extensive purplish reddish eruption involving the left infra-axillary region, extending to the shoulder posteriorly and to the middle of the left breast anteriorly. At first glance, the disease is suggestive of radiodermatitis; the skin is wrinkled, loose, shiny and interspersed with small telangiectatic macules. On closer examination, the skin appears velvety and furrowed, with many shiny polygonal umbilicated papules in evidence, especially at the borders. When the skin is stretched, the follicles are of normal color and intermingle with small pigmented macules. The right corresponding region and left upper part of the abdomen present smaller patches of a similar pattern but of a milder degree of inflammation. Itching is slight. The buccal mucosa shows Fordyce's disease, and a lipomatous mass is felt in the infra-axillary region. The patient underwent a hysterectomy in 1932 for a uterine fibroid. Menopausal symtoms appeared four years ago which were relieved by estrogenic therapy in the first part of 1946. The present condition began seven years ago in the left infra-axillary region as a small chafed area which gradually spread. The patient treated it continually without improvement until 1942, when she visited a local hospital, where a diagnosis of Hodgkin's disease was made. Thereupon a single dose of 275 r was given to the area involved. The following year a similar eruption appeared in the right axillary and abdominal region.

Biopsy revealed the classic picture of lichen planus except that the round cell inflammatory infiltration was continued downward around the blood vessels and appendages. Since the epidermis was atrophic in general, the lesion should perhaps be classified as atrophic lichen planus. An alternative diagnosis of lupus erythematosus could be excluded in view of the sharp demarcation of the subepidermal zone. In view of the distribution described clinically, it is fitting to consider whether this is a lichen-planus-like eruption due to drugs.

DISCUSSION

DR. DOUGLASS A. DECKER: I think that this is a classic case of poikiloderma atrophicans vasculare. There are telangiectasia, atrophy and pigmentation.

DR. CARROLL S. WIGHT: I agree with Dr. Decker. I could not find any typical lesions of lichen planus.

DR. DONALD M. PILLSBURY: I think that the case is one of lichen planus.

DR. HERMAN BEERMAN: The biopsy specimen I saw was suggestive of lichen planus. Clinically, however, I do not agree with the diagnosis of lichen planus.

DR. LOUIS GOLDSTEIN: With respect to the lesion on the left side, which was the original lesion, I admit that a diagnosis of poikiloderma might be right. However, the lesions on the other side surely have no resemblance to poikilo-

derma. The biopsy specimens were taken from both sides, and both were typical of lichen planus. A few years ago, the patient received a dose of roentgen rays, 270 r, to this area. That might have altered the picture.

Scleroderma with Phagedena of the Feet. Presented by DR. CARROLL S. WRIGHT and DR. M. H. SAMITZ.

C. de C., a white girl aged 17 years, wasted and decidedly undernourished, presents on the extremities, particularly the legs and feet, pronounced scleroderma with contraction of the fingers and toes. The feet show severe phagedenic changes with maceration and surface pyoderma. At the age of 11 the skin of the lower extremities had an abnormal appearance. It gradually tightened over the lower extremities, became pigmented, and in time the disease also involved the hands. Later the skin on the feet ruptured and became eroded and infected. The patient was studied at a New York hospital in 1942 and 1943 without benefit. Treatment has been symptomatic.

DISCUSSION

DR. JAMES T. FLOOD: I think that sympathetic nerve block would help relieve the pain.

DR. M. H. SAMITZ: The patient had a parasympathectomy performed several years ago without any benefit.

DR. CARROLL S. WRIGHT: I have not seeen this girl since last fall. She recently has had a course of treatment with penicillin, after which the lesions started to heal. For some reason the penicillin therapy was stopped and the lesions have become worse.

DR. C. C. THOMAS: I suggest the use of tyrothricin compresses.

DR. M. H. SAMITZ: I should like to suggest the topical use of thrombin. I know of three recalcitrant leg ulcers which showed amazing improvement with its use.

Dermatitis Herpetiformis. Presented by COMMANDER H. T. ANDERSON (by invitation):

Yaws (Tertiary). Presented by COMDR. H. T. ANDERSON (by invitation).

G. M. DeG., a well developed, well nourished Filipino man aged 23 years, in no distress, presents in the left palm, annular raised flat-topped lesions, 2 cm. in diameter. Hyperpigmentation is present in the center of the lesions. One is discrete; the others coalesce to form a cloverleaf. There are numerous scarred areas on the extremities, particularly the forearms and shins. On or about the first of April 1946, several itching papules developed in the left palm, which the patient burned with a cigaret to relieve the itching. The lesions then developed into rounded raised flat-topped papules. At the age of 13 he had similar lesions in the same site, which persisted for one year. He then received two injections of arsphenamine and one intragluteal injection, and the lesions healed promptly. He had tinea cruris (dhobie itch) at the age of 7 years, dysentery in childhood, malaria in 1943 and gonorrheal urethritis in November 1945. The result of urinalysis was negative. The Kahn reaction of the blood for syphilis was negative in June 1945, 4 plus on April 11, 1946 and 4 plus on April 18. A blood cell count revealed essentially normal observations.

DISCUSSION

DR. CLARENCE LIVINGOOD: Leprosy should be ruled out in this case.

DR. DONALD M. PILLSBURY: I think so, too. If that history is correct, the development was rapid with a definitely annular-papular lesion.

DR. HERMAN BEERMAN: I would venture the possibility of either erythema multiforme or granuloma annulare.

DR. HERBERT J. SMITH: Pardo-Costello said that yaws never becomes seronegative.

DR. DOUGLASS A. DECKER: The lesion was so hard that I wonder whether there was any possibility of cutaneous leishmaniasis.

DR. CLARENCE S. LIVINGOOD: The lesion does not resemble leishmaniasis.

A Case for Diagnosis: Localized Lymphedema. Presented by COMMANDER H. T. ANDERSON (by invitation).

Sebaceous Cyst with Xanthomatous Infiltration? Presented by DR. VAUGHN C. GARNER.

M. H., a well nourished white boy aged 1 year, presents a solitary, sharply circumscribed, pea-sized flattened nodule of striking canary yellow situated within the concha of the right ear. It had its onset about nine months ago as a pinkish nodule which a few months later became yellowish. The lesion is to be surgically excised.

DISCUSSION

DR. THOMAS BUTTERWORTH, Reading: I think that the disease is nevoxanthoendothelioma.

DR. DONALD M. PILLSBURY: I think that it is a sebaceous cyst with lipochrome pigmentation.

DR. VAUGHN C. GARNER: I thought of that possibility and considered it as an alternative diagnosis to nevoxanthomaendothelioma.

Lichen Planus Atrophicus? Lichen Sclerosus et Atrophicus? Presented by DR. CARROLL S. WRIGHT and DR. E. R. GROSS.

Lupus Vulgaris. Presented by DR. J. M. SCHILDKRAUT, Trenton.

Mrs. E. M., a Negro woman aged 27, presents a fused, yellowish brown, nodular eruption covering the nose and spreading over the right cheek. Over the nostrils the lesions are verrucous. There are patches on the right cheek, left malar area and left temple and at the corners of the mouth. On diascopic pressure the nodules are of the apple jelly type. The condition has been present for three years.

DISCUSSION

DR. C. C. THOMAS: I should like to point out the pronounced changes in the patient's fingers. The thumb and forefinger of the left hand and the forefinger of the right hand are decidedly fusiform and darkened. I think that roentgenographic studies would reveal interesting changes. The picture suggests the sarcoid type of tuberculosis.

DR. C. S. LIVINGOOD: I think that the patient has sarcoidosis.

NOTE.—A roentgenogram revealed cystic changes in the phalanges of the first, second and third digits of the left hand and of the second digit of the right hand. A roentgenogram of the chest revealed no abnormalities.